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Part I: ATTEMPTED SYNTHESIS OF BENZ-1-OXEPIN.

Part II: CYCLOHEPTENES FROM BICYCLIC PRECURSORS

SUMMARY.

Part I

Attempts were made to synthesise the unknown heterocyclic compound, benz-1-oxepin. Two separate ~~results~~ routes were investigated one involving the use of homochroman-3-one, the other, the use of the isomeric homochroman-5-one, both of which were reducible to the known homochroman. Homochroman-3-one was prepared by Dieckmann cyclisation of the dimethyl ester of dihydro-o-coumaroxyacetic acid, followed by hydrolysis and decarboxylation of the resultant β-keto-ester. The ketone was converted into the corresponding αβ-unsaturated compound which, on spectral evidence, failed to show any enolisation in basic solution. Homochroman-5-one, obtained by cyclisation of γ-phenoxybutyric acid, was treated in a number of ways in an attempt to insert the required double bonds. Work on the olefin, 2:3-dihydrobenz-1-oxepin failed to give the completely unsaturated system required. Both routes were characterised by the large number of by-products obtained at each stage and by the instability of intermediates and these factors almost certainly contributed to the lack of success.

Part II

2-(β-Benzoylethyl)-cyclohexanone was cyclised under acid conditions to 2-phenyl-bicyclo-[3.3:1]-non-2-en-9-one and

2-(β-benzoylethyl)-cycloheptanone, in a similar manner gave 7-phenylbicyclo-[4:3:1]-dec-7-en-10-one. The corresponding cyclopentanone derivative, 2-(β-benzoylethyl)-cyclopentanone, however, did not yield a bicyclic ketone under the same conditions. This reaction afforded instead an acidic material and an isomeric neutral compound, a γ-lactone. These were shown to be related by cyclisation of the acid to the lactone. The structures of the acid and lactone were examined and the acid shown to be 4-phenylcyclohept-3-ene carboxylic acid. A mechanism was proposed for the obtention of these compounds from the cyclisation of the diketone. 2-Phenylbicyclo-[3:2:1]-oct-2-en-8-one was itself obtained under suitable cyclisation conditions and was found to be very readily ring-opened under mild conditions to 4-phenylcyclohept-3-ene carboxylic acid and the corresponding γ-lactone. The reaction was shown to be applicable to a related diketone, β-(2-oxocyclopentylmethyl)-α-hydrindone, which yielded indeno(2',3':3,4)-phenylcyclohept-3-ene carboxylic acid.

PART I

Introduction

Note on Nomenclature.

Oxepins are members of the class heteropins, which are unsaturated seven-membered rings containing one or more atoms other than carbon. The corresponding fully saturated compounds are known as heteropans. The general formula for a heteropin (heteropin*e* where the heteroatom is N, or its analogues P and As) is as shown (1). In cases where maximum unsaturation occurs and the double bonds can be arranged in more than one way, the position of these bonds is defined by indicating the heteroatom or carbon atom not multiply-bonded and therefore carrying the "extra" hydrogen atom, e.g. 1H-, 2H-. (2) shows the structure of 2H- azepine.

Fusion of one benzene ring to the heterocyclic nucleus, giving the benzheteropin series, introduces the possibility of isomerism - for the heteroatom may now be in three different positions, giving the benz(o)-1-heteropins, benz(o)-2-heteropins and benz(o)-3-heteropins [of general structure (3), (4) and (5)].

Addition of a second benzene ring to the parent nucleus increases the number of possible isomers to four, giving dibenzo[b,f] heteropins, and the corresponding dibenzo[b,e], dibenzo[b,d] and dibenzo[c,e] systems. [(6) - (9)].

By far the greatest number of known heteropins contain, for the usual reasons, nitrogen, oxygen or sulphur, but it is interesting to note that other heteroatoms incorporated in the nucleus include both metals and non-metals. Compounds have been prepared with As[1], B[2], P[3], Se[4], Si[5], Sn(II)[6] and Sn(IV)[6] as the heteroatom.

Up to the present time none of the simple parent systems is known* (either synthetically or naturally-occurring), and of the totally unsaturated unsubstituted benzheteropins only benz-3-oxepin (10)[7] has been synthesised.** In the dibenzo series, as might be expected from the greater stability conferred on the compounds by the presence of two benzene rings, parent systems with X = O[8], S[9], NH[10] and BH[2] are known. Other heteroatoms occur mostly in the form of the tetrahydro derivatives and the bulk of all the work done on the class as a whole has been on derivatives of some sort.

This review will be confined predominantly to systems with a single heteroatom and their chemical history may be conveniently divided into two parts, pre-1950 and post-1950.

Pre-1950

In this period, heteropin chemistry presents a somewhat disparate appearance. The first example of the class (11),

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* See additional note 1 (p. 25)

** See additional note 2 (p. 26)

a derivative of dibenz [c,e] oxepin was recorded in the literature of 1877[11] but the second example (a derivative of dibenzo [c,e] azepine) was not recorded until 1888[12]. Yet another decade passed before the first monocyclic system, oxepan itself (12; X = O) was noted[13]. This compound and its sulphur analogue (12; X = S)[14], both readily prepared, excited no great interest since they possessed no unusual properties.

1911 marked a turning-point in heteropin chemistry. In this year a dibenz [b,f] oxepin derivative (13) was reported by Pschorr[15] as an abnormal by-product in an attempted phenanthrene synthesis. From this point on, the subject started to gather momentum and in the ensuing years derivatives of several other parent compounds appeared, including compounds derived from benz-1-oxepin (3; X = O), benz-3-oxepin (5; X = O), benz-2-thiepin (4; X = S) benz-3-thiepin (5; X = S) and from dihydro-oxepin. By far the largest number of compounds, however, were derivatives of tetrahydroazepine (hexamethyleneimine)[16] (12; X = NH). These were the subject of intensive research because of their potential usefulness in a variety of fields from analgesics and insecticides to adhesives, and although they are outwith the scope of this review, one relevant point may be noted. One of the earliest reactions carried out on tetrahydroazepine and some of its derivatives was an attempt to oxidise the reduced compounds to the unsaturated azepines[17]. The products isolated, however, were not azepines but derivatives of α-picoline.

Interest in the heteropin system stemmed also from another source, with the publication of Robinson's proposed structures[18] for strychnine derivatives, which incorporated a tetrahydro-oxepin nucleus. Following closely on this was the suggestion by Manske[19] that the alkaloid cularine (14) contained a dibenzoxepin ring system which gave unusual reactions. Oxidation of cularine derivatives was observed to give rise to xanthones. The latter compounds were not readily obtainable by other methods and as a result, part of the new interest in heteropins arose from their potential use as intermediates in the preparation of xanthones. In addition to this, cularine appeared to contain, in the dibenzoxepin system, a new type of ether linkage of biogenetic interest.

The benz-1-azepine nucleus (3; X = NH) was subsequently obtained[20] in rearrangement products of alkaloids of the *Erythrina* type and as a result, a considerable amount of work was carried out on the synthesis of benz-1-azepines as model compounds for these alkaloids.

So far, the naturally-occurring compounds mentioned above are the only ones known to contain a heteropin nucleus of some kind.

Up until 1950, therefore, heteropins were of interest solely on account of their pharmacological properties or because of their presence in novel naturally-occurring compounds.

Post-1950:

Suddenly and emphatically, however, this attitude changed and heteropins became keenly sought after as possible sources of verification and clarification of the Hückel Rule[21] and of the whole question of aromaticity in general.

The reason for this change possibly has its origin in the culmination at this time of all the work done in the field of azulene chemistry, coupled with the synthesis of tropolone[22] and derivatives (1950) and of tropone[23] itself (1951). Examination of the properties of the pseudo-aromatic azulenes and tropones stressed the need for determining the requirements for, and nature of, aromaticity in the seven-membered ring. Indeed, the whole question of aromaticity and in particular its relationship to the Hückel Rule has always aroused lively interest and heteropins appeared to provide another test case.

The concept of aromaticity and the importance of the "aromatic sextet" of electrons was originally developed to express some aspects of chemical behaviour of a certain class of molecule. It was first put in electronic terms in theories developed by Ingold[24] and by Robinson[25], and was subsequently shown to be compatible with the quantum physical aspect of the electron postulated by Hückel[21]. Once the connection between π-electron delocalisation and aromatic properties had been explained theoretically, it was recognised that aromaticity could be expected where conditions of stereochemistry, availability of orbitals and number of electrons allowed electron delocalisation to occur. This delocalisation of electrons is the most important factor in theories of aromaticity and the calculation of delocalisation energy is the chief aim of theories evolved to deal with it. This energy is decreased if the conjugated planar framework of the molecule is distorted into a non-planar conformation because maximum overlap of π-orbitals is then not possible.

From this it follows that the kind of atom involved in a π-electron system should not have an overwhelmingly detractive influence on its aromaticity, provided, of course, that it can supply a $2p\pi$-orbital and that it does not distort (e.g. by reason of size) the framework too seriously from planarity. Up to this point, there is no reason why heteropins should not exhibit aromaticity. It seems unlikely, however, (the writer believes), that they should have any light to shed on the meaning or validity of the Hückel Rule, a hope expressed fairly often by other workers. Indeed Hückel himself was careful to define the Rule's limitations. As originally stated[21] (1931) the Hückel Rule applied solely to monocyclic co-planar systems of trigonally-hybridised atoms which contain $(4n + 2)\,\pi$-electrons (where n is integral) and which would possess relative electronic stability. The rule is inherent in the form of the molecular orbitals which can be written for these systems and depends on the existance of degenerate molecular orbitals.

It has been recognised[26], however, that there are other systems not possessing a total of $(4n + 2)\,\pi$-electrons which are equally stable and presumably "aromatic". These are homomorphic systems (i.e. all participating orbitals have the same local symmetry) constructed from 2m orbitals. (For systems which obey Hückel's Rule $2m = 4n + 2$; in the above cases $2m = 4n$). These other systems include bicyclic and polycyclic compounds e.g. the tricyclic diphenylene which has twelve π-electrons. Not all systems with 4n electrons are as stable and non-benzenoid π-electron molecules show behaviour varying from olefinic (cyclo-octatetraene) through intermediate (azulene) to essentially aromatic (acenaphthene, ferrocene).

Acknowledging that the heteropin system would make a suitable topic for study in the light of what was already known about tropolones and azulenes, it was thought that a closer examination of other non-benzenoid systems could provide useful preliminary theoretical background. In the case of five-membered rings, the carbocyclic cyclopentadiene which is completely devoid of aromatic character contrasts sharply with the formally analogous heterocyclic aromatic systems furan, thiophen and pyrrole. The cyclopentadienyl anion, however, not only possesses an aromatic sextet but undoubtedly also the aromaticity which the parent hydrocarbon lacks.

In eight-membered ring systems, very little has been recorded of either the actual or theoretical properties of rings containing heteroatoms although the carbocyclic cyclo-octatetraene is very well documented[27]. The last two of the eight π-electrons occupy an unfilled state and Hückel Molecular Orbital Theory predicts that the planar molecule will be unstable. In practice, cyclo-octatetraene behaves as a highly unsaturated polyene with no aromatic character. The conformation adopted is the non-planar tub and the unsaturated character is due to the lack of conjugation between orthogonal double bonds; non-planarity alone, however, is not sufficient evidence that the eight π-electrons of the planar molecule would represent an unstable configuration, for the steric energy requirements of a planar eight-membered ring are expected to be substantial.

On the one hand then are the planar five-membered rings which possess (4n + 2) π-electrons and show distinct aromaticity; on the other is the non-planar, distinctly non-aromatic cyclooctatetraene with eight π-electrons. Between these two situations lie the seven-membered rings. The carbocyclic cycloheptatriene has three bonding molecular orbitals in two shells completely filled by six π-electrons which should therefore result in relative stability. The tropylium cation (15a) (with six π-electrons spread over several atoms) is stable; the radical (15b) with the odd electron placed in an anti-bonding orbital would be expected to oxidise readily, whilst in the anion (15c) the eighth π-electron is also placed in an anti-bonding molecular orbital and still leaves an incomplete shell. This anion, with eight π-electrons distributed over seven atoms is closest to the situation in heteropins and one might expect the stabilities of the systems to be of the same order.

It has been calculated[28], however, that introduction of a heteroatom into the tropylium anion π-lattice alters the degeneracy of the first anti-bonding molecular orbital and for electronegative heteroatoms lowers the energy. If the heteroatom is sufficiently electronegative, the fourth molecular orbital is bonding, but even in this case the highest occupied orbital has little bonding character and oxidation should be easy. Viewed in this light, the π-system of a typical heteropin has less stability than would be expected from a simple consideration of resonance structures. The only exception to this would be a system such as borepin which, with six π-electrons, would be expected to be stable.

In spite of theoretical predictions that heteropins would not be over-stable great efforts were made to synthesise not only the parent systems but benzheteropins and dibenzoheteropins. Apart from their own intrinsic interest, these latter were considered potentially useful for comparison with those of the corresponding derivatives of the tropone series. 2,3-Benzotropone (16), in contradistinction to tropone behaves as a typical dienone because fusion to the benzene ring reduces the gain in delocalisation energy obtained in going to the dipolar structure. Dibenzotropylium cations are very unstable due to steric interference of neighbouring benzene hydrogen atoms in a planar structure.

After 1950, therefore, the interest in heteropin chemistry was two-fold. The minor part was still concerned with attempted synthesis of model compounds for naturally-occurring heteropins. Here, of necessity, most of the work was carried out on dibenzo-derivatives containing a specific heteroatom. The major interest lay, and indeed still lies, in the properties of the parent systems, the particular heteroatom involved being initially immaterial.

For convenience, post-1950 research on heteropins may be classified under the three separate headings:-

1. Dibenzoheteropins.
2. Benzheteropins.
3. Parent heteropins.

1. Dibenzoheteropins

Although a great deal of work was done on these compounds most of it lies outside the scope of this review. A few compounds are worthy of note. Dibenzheteropins containing As[1], P[3], Se[4], Sn[6] were prepared but no mention made of their properties. Most interesting of all was a borepin[2] of structure (17) which with six π-electrons in the central ring, should show aromaticity. The smallness of the boron atom compared to, say, phosphorus or arsenic favours planarity and lack of strain.

The parent dibenzoxepin was synthesised by several workers[8], as was dibenzothiepin[9] (6; X = S). The latter is isosteric with 1,2:5,6-dibenzo-1,3:5,7 cyclo-octatetraene (18) and was found to have less olefinic character than the carbocycle.

2. Benzheteropins

Under this heading may be placed the most fruitful work from the point of view of providing information about the nature of heteropins.

The first compound prepared for study was a sulphur-containing seven-membered ring compound which Scott[29] postulated as 2:4-dicarboxybenz-3-thiepin (19; X = S, R = CO_2H) and therefore containing a system of double bonds formally analogous to thiophen. He stated that instability prevented the preparation of acid derivatives or of reduction products. A model of the compound showed it to be strained and non-planar. The same compound was later prepared by Dimroth and Lenke[30] and converted to the more stable di-ester (19; X = S, R = CO_2CH_3) which showed an appreciable degree of aromatic character. The same general behaviour was manifested by the nitrogen analogue (19; X = NR') prepared by Dimroth and Freyschlag[31]. The properties of the nitrogen and sulphur analogues were such as to make the oxygen-containing compound even more interesting. It is possible that stereochemistry may be involved in the respective stabilities. The oxygen atom is smaller than the carbon atom but the valency angles are not dissimilar.

Therefore of the unsaturated seven-membered heterocyclic rings, the oxygen-containing one must be the one in which the ring is nearest planarity. It is also possible that with the help of the oxygen atom unbound electron pairs may be stabilised by resonance. In addition molecular orbital calculations predict that oxygen, by virtue of its larger electro-negativity will exert a stabilising effect on the anti-bonding orbital containing the fourth electron-pair, lowering the energy relative to that of azepine and thiepin, so that it approaches a bonding orbital in energy.

Dimroth and Freyschlag accordingly prepared the oxygen di-acid[32] (19; X = O, R = CO_2H) and found that among other aromatic-like properties it possessed stability to mineral acids (incompatible with its representation as a classical divinyl ether). This work was later called into question by Schönberg and Fayez[33] who criticised both this and Scott's original work on the sulphur acid (19; X = S, R = CO_2H) and refuted the claim that the seven-membered ring "approached" an aromatic system. Schönberg and Fayez held the opinion that the properties of the sulphur-containing di-acid were more like those of a sulphide and accordingly proposed the structure (20).

After considerable disagreement the whole question appears to have been cleared up recently by Jorgenson[34] who re-investigated the work already done. In an extremely lucid paper Jorgenson confirmed the remarkable stability to acid and explained it on the basis of formation of a protonated species in which the ~~benz~~ benzoxepin ring as a whole acts as a protonation site, affording an aromatic sextet; the most likely site seemed to be the oxygen atom itself since other sites are too close to the carboxyl groups.

Of the benz-2-heteropins only the oxygen analogue has received any attention and only in the form of saturated derivatives. In the benz-1-heteropin series a similar situation exists, the known compounds being all derivatives of the tetrahydro system.

3. Parent Heteropins

In recent years, a considerable amount of work has been carried out on the parent systems, notably with oxygen as the heteroatom. Much of this has been done by Meinwald[35] and his collaborators. They (and Olsen and Bredoch[36] independently) prepared 2, 3: 6, 7-tetrahydro-oxepin (21) which it was hoped to convert to the 2, 7-dihydro derivative (22). The compound obtained actually proved to be the 2, 3-dihydro-oxepin (23). The synthetic objective here and in the work of others was the epoxy-diene (24) which is the valence tautomer of oxepin, and assumed to be thermally convertible into the latter. There were indeed previous analogies for this, but so far* the idea has not met with much success.

Weston[37] claimed that he had synthesised an oxepin of structure (25) by direct condensation of acetonylacetone and cyanoacetamide to give a compound he assumed to be 2-amino-4,7-dimethyloxepin-3-carboxamide (26). This was subsequently shown by Buchanan and Hamilton[38] to be the compound (27) with which the reported properties were much more compatible.

In the case of sulphur-containing compounds, Traynelis and Lowe[39] prepared both sulphides and sulphones to test for the presence or absence of aromatic properties in such systems. The sulphones may be regarded as analogues of tropone which can give rise to the stable cation (28). Here the sulphonyl group by electron attraction and possible participation of vacant d orbitals can help delocalisation of six π-electrons over seven atoms (29a) $\leftrightharpoons$ (29b). The question of the importance of this stabilisation in the absence of planarity has been raised. An attempt by Maerov[39] to synthesise the parent sulphone produced an unstable compound. This, if it was the desired product, was certainly not resonance stabilised.

Of the nitrogen analogues N-carbethoxyazepine[56] (1; X = $NCO_2C_2H_5$)[19] the nearest compound to the parent system yet prepared. A compound of structure (30) has been made but attempts to desulphurise it proved unsuccessful.[40]

Before embarking on a synthesis of a heteropin system it would seem a sensible approach to review the relevant properties of compounds already obtained as well as their method of synthesis since information gained from these could indicate what form future work should take and what would be a reasonable synthetic objective.

General Properties of Heteropins

1. Dibenzheteropins:

Only the unsaturated compounds provide any useful information. Of the parent systems the dibenzoborepin (17)[2] appears to be relatively stable (although this does have six π-electrons).

2. Benzheteropins:

Although there has been some controversy about both the structures and properties of some of these compounds, some general trends may be observed.

(a) Benz-3-heteropins:

The general structure of these compounds is as shown (19). In general, dicarboxylic acid derivatives ($R = CO_2H$) are unstable and resinify readily while the di-esters are more stable, even resisting attack by concentrated sulphuric acid. Quite a degree of difference of chemical behaviour is shown by individual compounds:-

(i) $X = NCH_3$, $R = CO_2CH_3$[31]

This loses nitrogen in alkali, has the heterocyclic ring oxidised by permanganate and is reduced by hydrogen over palladium-barium sulphate. On the other hand it does not add either diazomethane or methyl iodide, while bromine adds to the nitrogen atom and not to the double bond. The corresponding acid ($R = CO_2H$)[31] is stable to perchloric acid indicating that an aromatic cation is formed in the presence of electrophilic reagents.

(ii) $X = S$, $R = CO_2CH_3$[30]

In alkali, this decomposes with loss of sulphur, while in acid, naphthalene dicarboxylic acid is obtained. Thermal decomposition also results in extrusion of sulphur, to give naphthalene. Unlike the corresponding nitrogen compound, the sulphur ester adds diazomethane to give a pyrazoline-like adduct, but an appreciable degree of aromatic character is manifested by the same general behaviour as the nitrogen compound.

(iii) $X = O, R = CO_2CH_3$

This ester[32] is stable to mineral acid and enters reluctantly into reactions with bromine and permanganate. One double bond is readily reduced catalytically, but the second only with difficulty. Methanol is not added under conditions in which enol ethers usually react to give acetals.

The corresponding acid ($R = CO_2H$)[32] is extremely stable to acid due to protonation on the oxygen atom.

From the known properties, it may be concluded that the oxygen analogues are the most aromatic in character. This is in accord with theoretical predictions.

(iv) $X = SO_2, R = H$

The non-aromatic character of this molecule[41] was established by its susceptibility towards addition reactions, by thermal instability and by difficulty in forming it by dehydrogenation. A model of the molecule, however, showed it to be distinctly puckered.

(b) Benz-2-heteropins:

No properties of these have been reported.

(c) Benz-1-heteropins:

These are of general structure (3).

(i) $X = NCH_3$

The derivative of the system shown (31) appears to be the only one whose properties have been investigated. It is reported[42] as being unstable and insufficiently reactive to give ketonic derivatives.

(ii) $X = SO_2$

This compound[39] shows more stability than the isomeric sulphone in (a) (iv) above, and does not in general behave like an ordinary αβ-unsaturated sulphone. Although the dihydro derivative adds bromine readily, the parent sulphone will do so only in sunlight or U.V. light. The U.V. spectrum indicates some extended conjugation. On balance, the results suggest an appreciable degree of olefinic character in the heterocyclic ring.

No particular properties of any benz-1-oxepins or benz-1-thiepins have been noted.

3. Parent Heteropins:

These are of the general structure already shown (1). The only system so far known* is that with $X = SO_2$ and

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* See Additional Note 1.

there is some doubt as to whether this compound was actually produced. If it was, it was unstable and obviously not resonance stabilised[39].

Previous Methods of Synthesis.

The principal methods of synthesis can be divided into three categories:-

(a) ring closure,
(b) ring expansion,
(c) condensation of appropriate fragments.

1. Dibenzheteropins.

(a) These have been prepared by cyclisation of carbonyl compounds[43,44], and by formation of lactones and lactams[45] followed by reaction of the carbonyl group. In the case of the oxygen analogues, an additional synthesis[46] was provided by the Ullmann method for preparation of diphenyl ethers.

(b) Oxygen-containing compounds have been prepared by expansion of xanthene derivatives[8].

2. Benzheteropins.

(i) Benz-3-heteropins:

(a) An example of a ring closure method[47], using a carbonyl compound is as shown (32) —> (33).

(c) The chief synthetic method[29,30,31,32,33], which is a general one, consists of condensation of o-phthaldialdehyde and the 2,2'-heterodiacetic ester (34) to give the corresponding substituted heteropin as shown (19). The Wittig reaction was employed in the preparation of unsubstituted benz-3-oxepin (19; X = O, R = H)[7] by the reaction scheme shown. (Scheme A).

(ii) Benz-2-heteropins.

(a) One of the few successful reactions[48] in this series was ring closure of the alkyl halide (35) to the saturated tetrahydrobenz-2-oxepin (36).

(iii) Benz-1-heteropins:

(a) Cyclisation of the appropriate carboxylic acid (37) has yielded derivatives of benz-1-oxepin and benz-1-thiepin but with nitrogen as the heteroatom the cyclisation could not be induced to take place[49]. Lactam formation and Dieckmann cyclisation (e.g. (38) ⟶ (39)) have also been employed, in addition to other methods of less general use.

(b) The only ring expansion noted so far has been the rearrangement of sulphonates (e.g. (40) ⟶ (41)), a method which appears to be a limited application[50].

(c) Another method of limited application[51] has been the condensation of an arylamine with a γ-keto-acid (exemplified by (42)→(43)).

3. Parent Heteropins.

(a) A successful method[52] of ring closure has been the cyclisation of a bromo-acetate (of type (44)) to a substituted 4,5-dihydro-oxepin (45) while unsubstituted 4,5-dihydro-oxepin itself has been prepared[53] by the cyclisation of the diene shown (46), obtainable from the readily available acrolein.

(b) Several methods of ring expansion have been used in the preparation of the parent heteropin systems. The most important are as under:-

(i) treatment of cyclic ketones with diazomethane (e.g. expansion of (47)→(48)).

(ii) pyrolysis of phenylazide in primary aryl amines[54] to give the appropriately substituted azepine (e.g. (49)→(50)).

(iii) Via carbene intermediates. This method has been tried by several workers[55] with, so far, little success. (e.g. see reaction scheme (51)→(52))

(iv) Via nitrene intermediates[56] (see (53)→(54)).

Choice of Synthetic Objective:

Benz-l-oxepin (3; X = O) was chosen as the synthetic objective for the study of a particular example of a heteropin. The reasons for this were three-fold:-

1. Dibenzo derivatives cannot be expected to give a true picture of the properties of the heterocyclic ring. The benz derivative, however, while lending extra stability to the system does not interfere so much with these properties. In the fused benzene ring system one of the three double bonds required in the heterocyclic ring is already present. The benzheteropin, in addition, could serve as a useful model compound for the parent heteropin itself which would be the ultimate objective of any study such as this.
2. Oxygen was chosen as the heteroatom in the light of previous experience. Its size and large electro-negativity render it the most useful of the hetero atoms since the product is likely to be nearly planar and stabilised by resonance.
3. The choice of position of the hetero-atom adjacent to the benzene ring was influenced by the possibility of extended conjugation, by the fact that less appears to be known about the properties of benz-l-heteropins, and by

an interest in the potential products of ring collapse. In the event of ring contraction the oxygen may stay attached to one position or the other, producing either α-naphthal or a compound with oxygen at the bridgehead.

Additional Note 1

Vogel has recently reported[57] the first successful synthesis of a parent heteropin - the oxygen analogue (1; X = O). This was achieved via the valence tautomer (24) which other workers had failed to obtain.

Cyclohexa-1,4-diene (55) is converted to the mono-epoxide (56). Bromination and dehydrobromination of the latter gives the diene-epoxide (24) which on heating isomerises to oxepin. The product appears to be very unstable, rearranging readily to phenol as expected.

Additional Note 2.

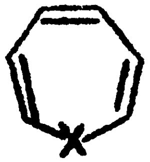
A successful synthesis of benz-l-oxepin has recently been reported by Sondheimer and Shani[58], involving again the use of valence tautomers which it was suspected would be the eventual solution to this and similar problems.

Elegant in its simplicity, the synthesis had as its starting point the epoxide (57). Bromination of both double bonds followed by dehydrobromination in ethanolic potassium hydroxide gives two products (3; X = O) and (58) in 20% and 50% yield respectively. These are both postulated as having come from the same valence tautomer (59) by the appropriate mechanistic routes shown; they are presumed to be derived differently since (3; X = O) and (58) are not interconvertible by base.

The properties of the two products are of particular interest since the structure (58) has ten π-electrons and the structure (3; X = O) has eight π-electrons in the heterocyclic ring. The compounds might therefore be reasonably expected to behave differently.

(58) is shown to be aromatic in character from the following observations. The n.m.r. spectrum shows bands at very low field (centred at 2.52τ) indicative of a ring current. The compound also undergoes aromatic-like electrophilic substitution.

Benz-1-oxepin itself (3; X = 0) is reported as a low-boiling liquid whose n.m.r. spectrum indicates that the substance is olefinic in character. On catalytic reduction, the compound yields homochroman (60).



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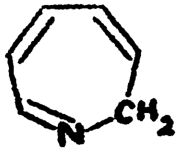

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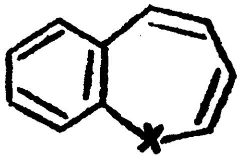

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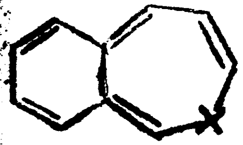

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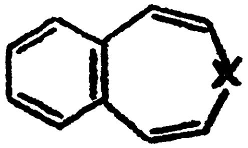

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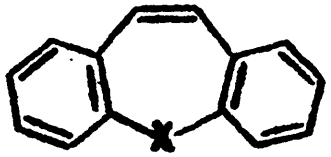

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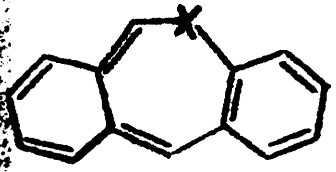

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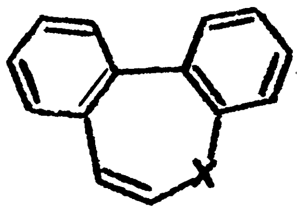

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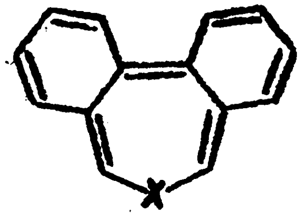

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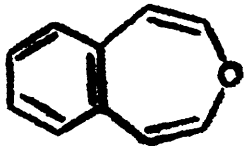

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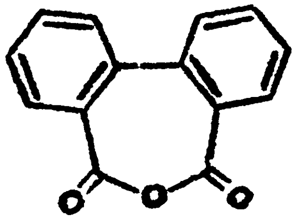

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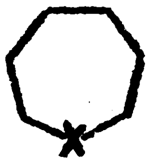

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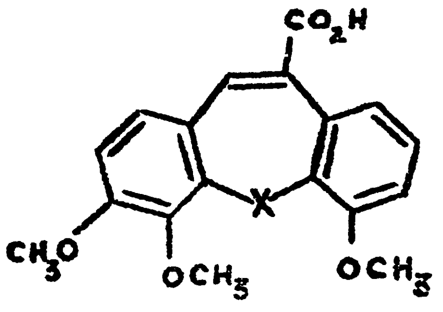

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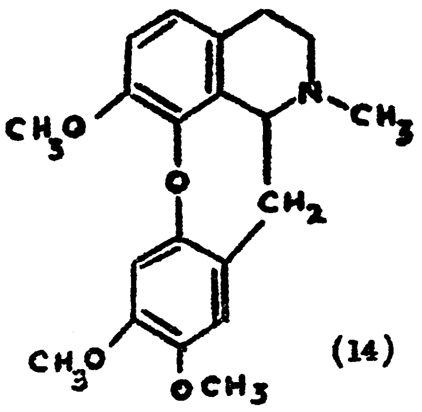

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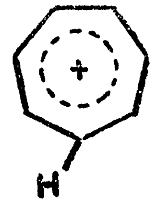
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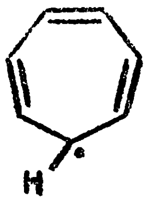
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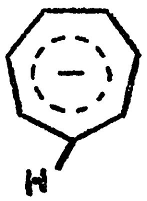
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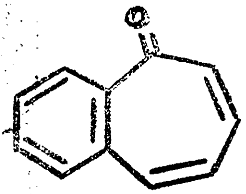
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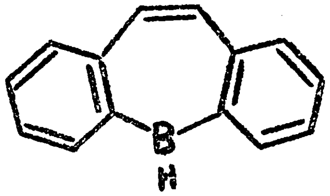
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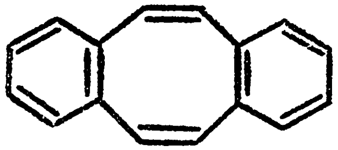
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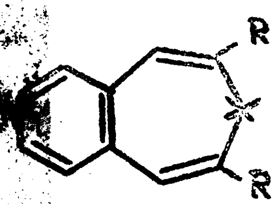
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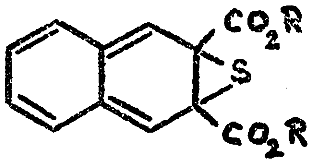
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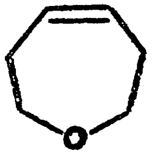
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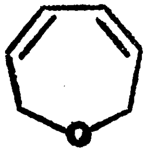
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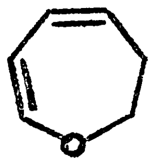
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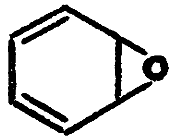
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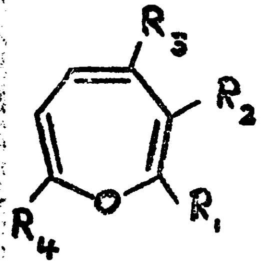
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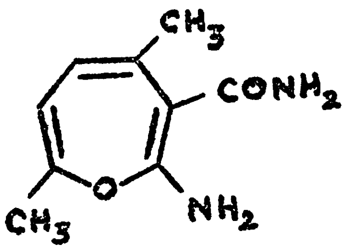
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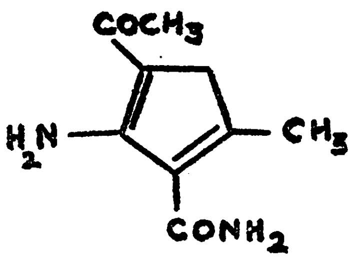
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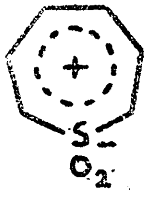
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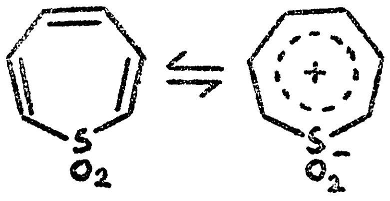
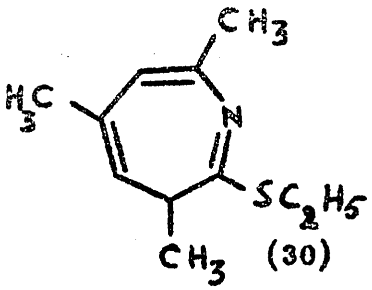

(29a) (29b) ≡ (28)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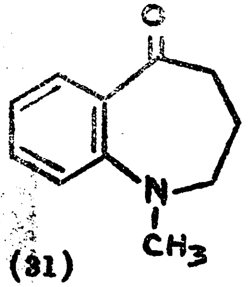
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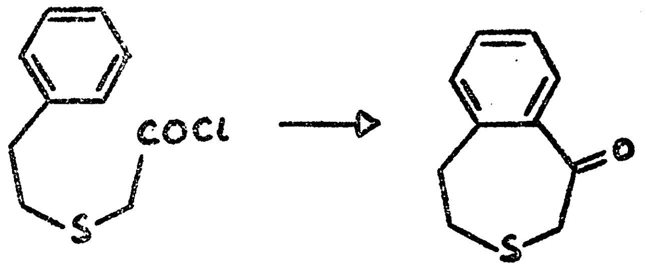
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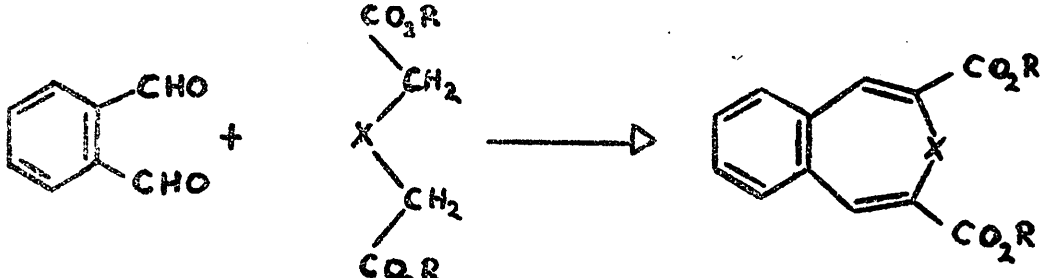
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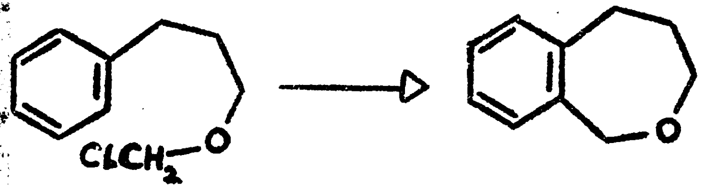
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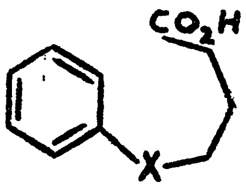
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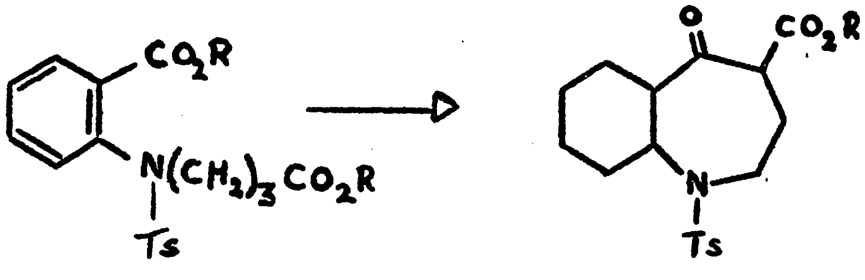
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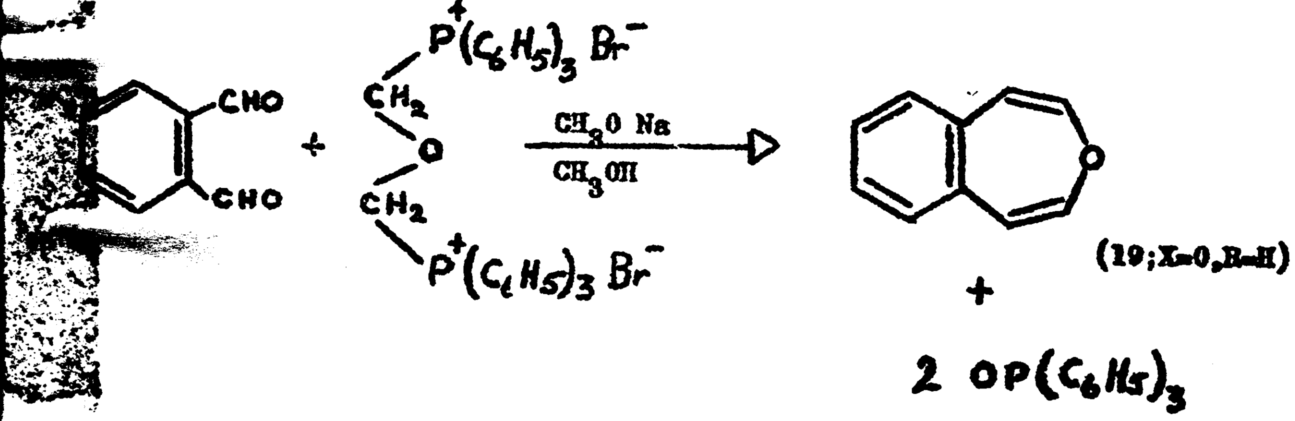
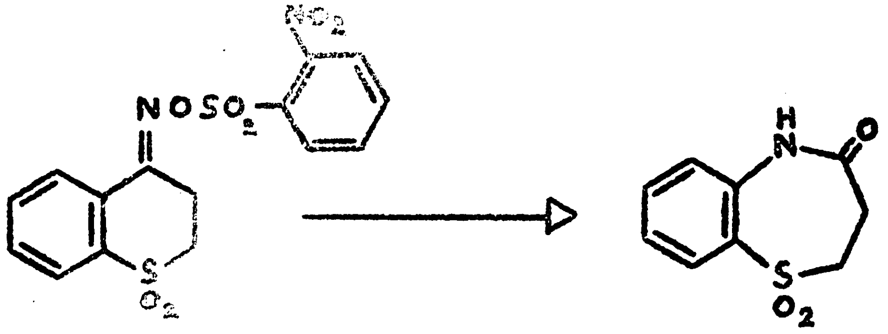
SCHEME A



(19; X=O, R=H)



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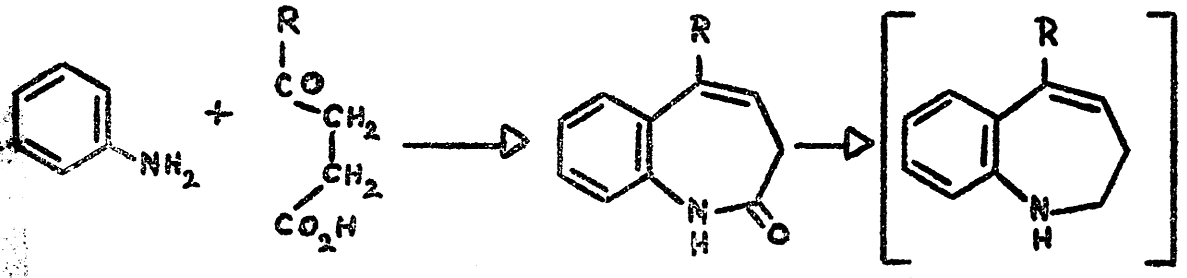
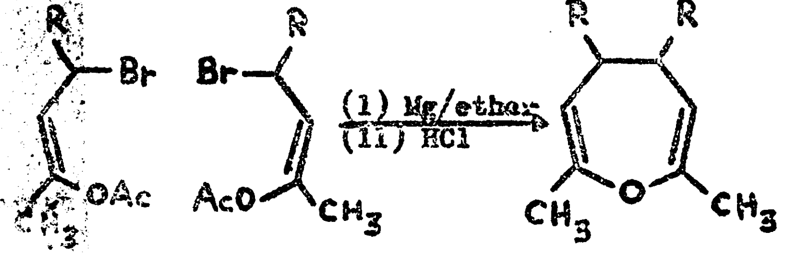
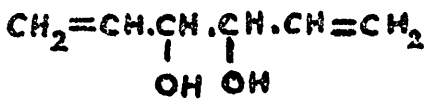


(42) (43)

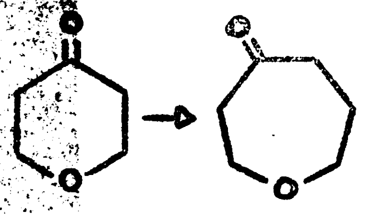


(44) (45)



$$CH_2{=}CH.\underset{OH}{CH}.\underset{OH}{CH}.CH{=}CH_2$$

(46)



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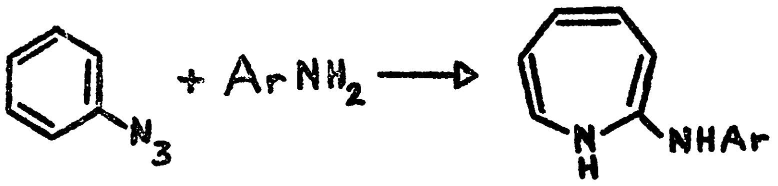
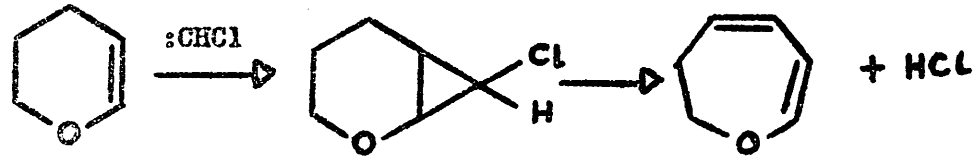


(49) (50)



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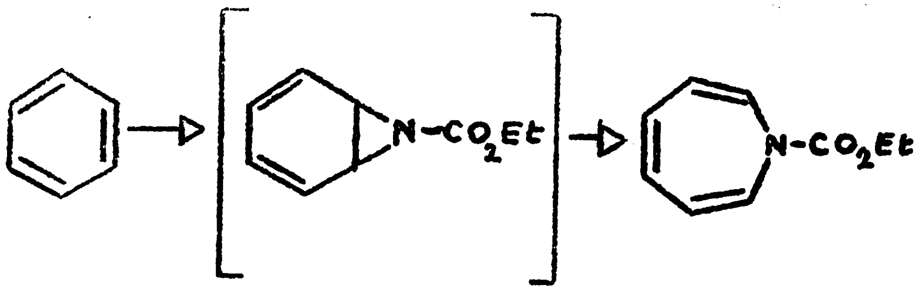

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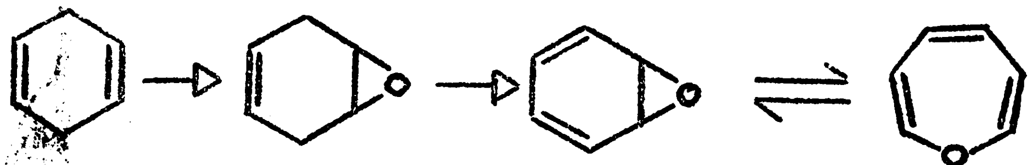
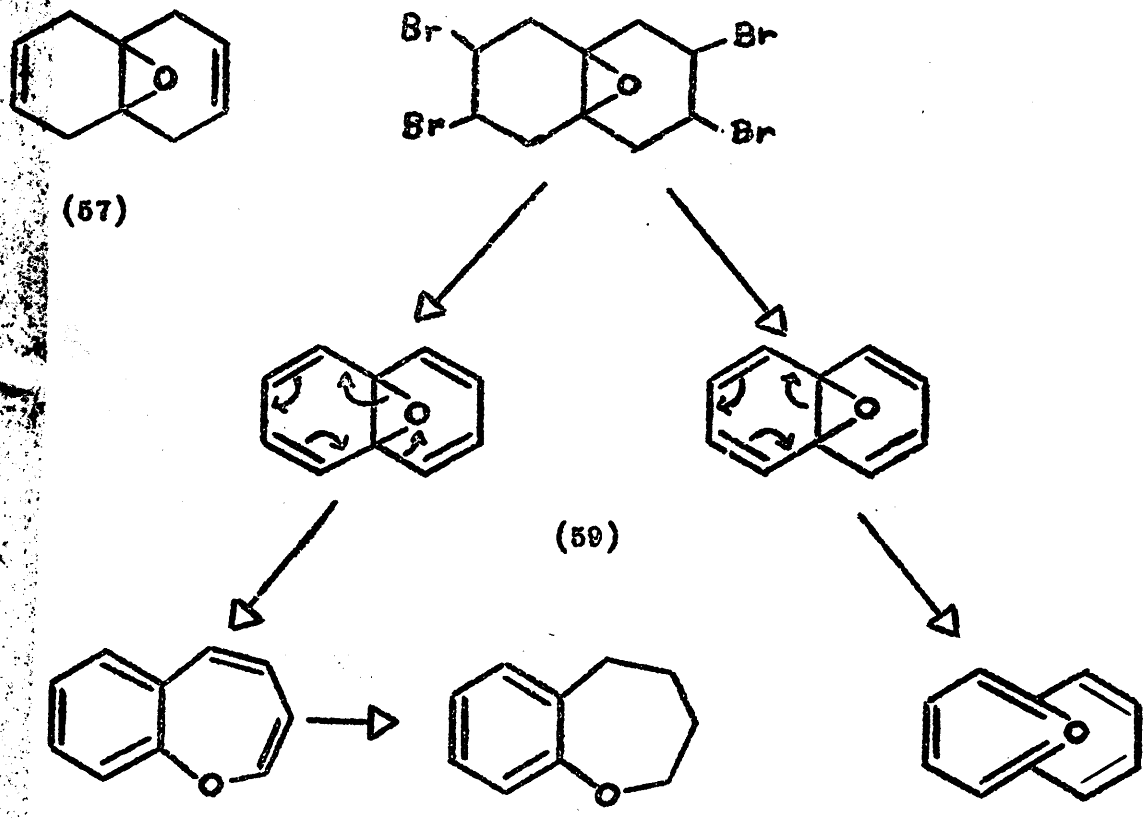


(55) (56) (24) (1;X=0)



(57)

(59)

(3;X=0) (60) (58)

DISCUSSION

It was intended that the synthesis of benz-1-oxepin (3; X = 0) should be approached via two different routes. In each case there was a key intermediate, potentially useful in several ways for the insertion of the appropriate double bonds. In addition, the routes planned were such that the intermediates could be related to each other.

In route A, the desired intermediate was homochroman-3-one (2,3 : 4,5-tetrahydrobenz-1-oxepin) (61), a potential product from pyrolysis of the barium salt of dihydro-o-coumaroxyacetic acid (62). The latter it was hoped to obtain from readily available salicylaldehyde, by extension of both functional groups, firstly to o-formylphenoxyacetic acid (63). This should then give, via the Perkin reaction or via a Knoevenagel reaction with malonic acid, o-coumaroxyacetic acid (64), reducible to the required diacid (62).

Alternatively (route B), it would be possible to use the known isomeric homochroman-5-one (65).

Correlation of the routes should be available by the reduction of both homochroman-3-one (61) and homochroman-5-one (65) to the same compound, the known homochroman (60).

Route A.

Some difficulty was experienced at the commencement of this route. The instructions given in the literature[59] for Katz's preparation of o-formylphenoxyacetic acid (63), when carried out exactly as stated, gave none of the required product, but with drastic alterations to the given reaction time a low yield of the acid was obtained. It is therefore possible that a misprint has occurred.

In the first instance, a mixture of chloracetic acid, salicylaldehyde and aqueous sodium hydroxide was refluxed for twenty hours (Quantities used and reaction time were as reported in the literature). The reaction mixture did not become homogeneous and it was noted that the aqueous layer was acidic to litmus instead of alkaline as expected; further portions of chloracetic acid and sodium hydroxide were therefore added and the mixture became homogeneous. Acidification yielded an oily solid which was soluble in aqueous sodium carbonate. Reprecipitation of the acidic material gave a fine yellow solid and a brown oil which solidified on cooling. The yellow solid was soluble in hot water, the brown oil insoluble, and separation of the two components was effected by filtration of the hot aqueous solution. The filtrate, on cooling, gave a yellow amorphous material, m.p. 165° and 178°. (o-formylphenoxyacetic acid has m.p. 133°). On admixture with an authentic sample of (63), a marked depression of the m.p. was observed. An i.r. spectrum of the amorphous material showed complete absence of aldehyde absorption; but indicated the presence of an aryl carboxylic acid (ν max 1680 cm^{-1}), an aliphatic carboxylic acid (ν max 1742 cm^{-1}) and ortho-substitution in the benzene ring (ν max 765 cm^{-1}). Later work (see p. 33.) showed that the material was in fact, predominantly o-carboxyphenoxyacetic acid (66). This may have arisen either by oxidation of the corresponding aldehyde or via a Cannizzaro reaction due to prolonged heating in base. The latter possibility would also account for the obvious mixtures obtained from the reaction, Cannizzaro reactions being possible on both the starting aldehyde and the product aldehyde.

Since prolonged heating was obviously undesirable it was considered possible that the reaction time given in the literature should have read "2 hours" and not "20 hours". The reaction was therefore repeated, with a reflux time of two hours and gave a 12% yield of the required acid (63) m.p. 129-131°.

A yield of this order being an obvious disadvantage for a starting material, an alternative preparation of the acid was attempted, following Zubrys and Siebermann's modification[60]. The acid was readily obtained in 57% yield, m.p. 130-133°. The i.r. spectrum was notable for the presence of three carbonyl bands instead of the expected two. An unusually sharp hydroxyl band accompanied these. The apparent anomalies may be accounted for in terms of hemiacetal formation between the aldehyde group and the hydroxyl of the carboxylic acid group $(63) \longrightarrow (67)$. The carbonyl bands can then be assigned as follows:- ν max 1750 cm^{-1} (δ-lactone of hemiacetal), 1710 cm^{-1} (aliphatic carboxylic acid), 1670 cm^{-1} (aryl aldehyde) while the band at 3150 cm^{-1} may be attributable to the hydroxyl group of the hemiacetal form.

The next stage in the proposed synthesis likewise presented some literature difficulty. Rössing's method[61] was followed for the attempted preparation of o-coumaroxyacetic acid (64). This involved a reaction of the Perkin type between o-formylphenoxyacetic acid (63) and a mixture of acetic anhydride and sodium acetate in the weight ratio 1: 5-6: 3. Rössing isolated an acid from the reaction mixture which he claimed was the acid (64). He reported a m.p. of 197° and an analysis of the silver salt giving Ag, 49.62% (Required: Ag, 49.54%). The acid, according to Rössing formed a dibromide.

In our case, a small pilot run gave a minute amount of an acid, m.p. 197°. In a repeat procedure, larger quantities were used and resulted in an 11% yield of an acid with an anomalous m.p. (softening at 145°, m.p. 177-180°) even after repeated crystallisation from water. The i.r. spectrum of this acid, however, corresponded to that of the product from the initial attempt. Yet another attempted preparation on a considerably stepped-up scale yielded an acidic compound (40%) whose i.r. spectrum was completely different from that of the initial acidic product. This new acid could be recrystallised from hot water as a pale yellow solid, m.p. 225-227°. Analysis showed the acid to have the empirical formula $C_{11}H_{10}O_5$. The i.r. spectrum showed two carbonyl frequencies, increased intensity of double bond absorption in the 1620 cm^{-1} region and a new band at 990-980 cm^{-1} (trans-disubstituted double bond).

The acid obtained by Rössing and in our own first two attempts was then shown to be not the required acid but coumarilic acid (68). A sample of the latter was prepared by the standard method[62] from coumarin via the corresponding dibromide. It was obtained as a crystalline solid (m.p. 190.5°) whose i.r. and u.v. spectra were identical with those of "Rössing's acid". No depression of m.p. was observed on admixture of "Rössing's acid" and authentic coumarilic acid, whereas the m.p. of a sample of the acid m.p. 225-227°, mixed with coumarilic acid was considerably depressed.

It must be admitted that Rössing did not have the advantage of modern physical techniques and in fact, all the reactions he quotes for his acid could be given equally well by o-coumaroxyacetic acid. As additional evidence for the structure of the acid m.p. 225-227°, reductive and oxidative reactions were carried out.

Coumarilic acid was reduced catalytically to dihydrocoumarilic acid (69), m.p. 116.5°; the unknown acid m.p. 225-227° on reduction gave a white crystalline acid m.p. 146° whose i.r. spectrum showed no isolated double bond absorption. A marked depression in m.p. was observed on admixture of the two reduced acids.

Alkaline potassium permanganate oxidations were carried out on each of the following acids and a comparison made of the products.

(a) o-Formylphenoxyacetic acid (63) on oxidation gave an 80% yield of o-carboxyphenoxyacetic acid (66), m.p. 190-191.5°.

(b) "Rössing's acid" on oxidation gave
  (i) with mild heating;- unchanged starting material;
  (ii) with prolonged heating;- no extractable product.

(c) Authentic coumarilic acid on oxidation yielded
  (i) under mild conditions:- unchanged starting material;
  (ii) under vigorous conditions:- carbon dioxide and water only.

(d) The acid m.p. 225-227° on oxidation gave a 50% yield of an acid m.p. 189°, shown to be o-carboxyphenoxyacetic acid.

A mixture of the products from reactions (a) and (d) showed no depression of m.p. and the i.r. spectra of the two acids were identical in all respects. By contrast, on admixture of the products from reactions (a) and (b)(i), the m.p. was considerably depressed and the i.r. spectra did not correspond.

It may be concluded from the above that "Rössing's acid" was coumarilic acid which on reduction gave dihydrocoumarilic acid and on oxidation was unaffected by mild conditions but completely destroyed under vigorous conditions. The unknown acid m.p. 225-227° was, however, the required o-coumaroxyacetic acid (64). Both physical and chemical properties were in accordance with the expected structure. (See Experimental).

As a method of synthesis, the Perkin reaction proved unsatisfactory in this particular instance and an alternative condensation of the Knoevenagel type was investigated. o-Formylphenoxyacetic acid was condensed with malonic acid in pyridine, using piperidine as the condensing agent. Small-scale reactions, as in the case of the Perkin reaction, yielded coumarilic acid (23%) while large-scale reactions with a short reaction time gave the required o-coumaroxyacetic acid (in 71% yield).

It would therefore appear that reactions carried out on a small scale with a relatively long reaction time resulted merely in intramolecular dehydration of o-formylphenoxyacetic acid to coumarilic acid while under milder conditions, a true intermolecular condensation could take place.

Reduction of the acid, in bulk, was carried out not with palladium-charcoal as catalyst, but using Raney nickel, with hydrogen under pressure. The reduction was carried out in aqueous sodium hydroxide and it was found that on acidification of the reaction mixture two products were obtained. At pH 7-8 a crystalline solid was precipitated. This was the required dihydro-o-coumaroxyacetic acid. The product was identical with that given by the palladium-charcoal catalysed reduction, did not decolourise alkaline potassium permanganate, nor did it show any double bond absorption (other than aromatic) in its i.r. spectrum. At pH 4 another crystalline solid was precipitated and proved to be half-hydrogenated diacid, with an indefinite m.p. and showing some double bond absorption in its i.r. spectrum. The acidification of the reaction mixture thus provided a means of obtaining dihydro-o-coumaroxyacetic acid uncontaminated by unreduced starting material, in cases where reduction did not go to completion. Optimum conditions for loading the apparatus were eventually worked out by trial and error so that reduction was carried out to completion before pyrolysis was attempted.

The first application of barium salt pyrolysis as a method of ring closure was by Boussingault[63] in 1836. He obtained cycloheptanone from pyrolysis of the barium salt of suberic acid. To-day the method is still essentially the same. Pyrolysis leading to seven-membered rings is known to be difficult and to result in low yields, partly due to the strain involved and partly due to formation of by-products. (It was for the former reason that (62) was chosen for use in pyrolysis, rather than the double-bonded acid (64). Although the unsaturated acid on cyclisation would already have one of the required double bonds present, ring closure was presumed to be more feasible in the saturated compound). Other workers have used calcium, yttrium and thorium[64] salts in preference to the barium salt; it ~~has~~ recently been found[65], however, that a catalytic mixture of iron filings and 5% baryta gives cleaner products. In this instance, pyrolysis was carried out on the dry barium salt itself. The first attempt, in which the diacid and barium carbonate used were in a molar ratio of 1: 2.5, afforded mainly unchanged starting material, but accompanied by a phenolic product and a neutral material.

The phenolic product consisted of a brown oil which could not be induced to crystallise. It was identified as phenol itself by comparison of i.r. spectra and conversion into the known tribromophenol.

The neutral material was shown to be a mixture of the lactone dihydrocoumarin (70) and its corresponding hydroxy-acid, melilotic acid (71), by comparison with authentic samples. Hydrolysis of the lactone gave the free acid (71) but attempted recrystallisation or distillation resulted in partial relactonisation and a mixture of (70) and (71) was obtained. This ready interconversion was also found to occur in known samples.

An increase in the proportion of barium carbonate to acid (5:1) in preparation of the barium salt was found to be efficacious and no unchanged starting material was obtained under these conditions.

It is difficult to postulate any satisfactory mechanism for the formation of phenol and dihydrocoumarin during the pyrolysis. These two compounds must have been derived either from the starting material or from the ketone (61), assuming it is first formed. Although other explanations are possible, the most likely invokes cleavage of the ether linkage in the starting material. Although at the temperature of the pyrolysis this could no doubt be done in other unspecified ways, one possible mode of cleavage is as shown (Scheme B). The intermediate could then be imagined as giving rise to phenol (Scheme B_1) or to (70) (Scheme B_2). It is much more difficult to provide a reasonable mechanism by which the observed products could have come from the ketone (61).

In an attempt to clarify the situation, however, the pyrolysis was repeated, incorporating into the system a cold-trap for isolation of any volatile fragments from the reaction. No new compound was isolated, the only materials found in the trap being traces of phenol and dihydrocoumarin.

In view of the results obtained from pyrolysis, an alternative method of cyclisation was sought. Dieckmann closure of the diester of dihydro-o-coumaroxyacetic acid (62) should give the β-keto-ester (72a) or the less probable isomer (72b), either of which, on hydrolysis and decarboxylation should yield the required ketone (61). The β-keto-ester itself is also potentially useful for the insertion of double bonds into the heterocyclic ring.

The dimethyl ester of the acid was readily obtained by treatment of the acid with diazomethane, but on a preparative scale it was found more practicable to form the ester by treatment with anhydrous methanol and concentrated sulphuric acid. This afforded the ester in 82% yield whereas the standard Fischer-Speier method which was also investigated gave only a 57% yield in return for a more tedious preparation.

Cyclisation of the diester (73) by the Dieckmann method was attempted using various modifications (as noted below) until optimum conditions were found. Hydrolysis and decarboxylation of the products in each case was also carried out.

(a) A high dilution technique in refluxing xylene, using sodium hydride as condensing agent, gave a neutral product in 47% yield. This consisted of a brown viscous oil whose i.r. spectrum showed the distinctive characteristics of a β-keto-ester. The oil gave the expected intense purple colouration with methanolic ferric chloride. The crude product was subjected to base hydrolysis and acid-catalysed decarboxylation and afforded both acidic and neutral materials. The former was found to be a mixture of melilotic acid (71) and the corresponding lactone (70) while the latter was the required ketone homochroman-3-one (61), characterised as its 2:4-dinitrophenylhydrazone. The overall yield of the ketone by this method was 28%. The presence of (70) and (71) could be accounted for if it were assumed that some unchanged diester (73) remained in the β-keto-ester. (73), on hydrolysis would give the di-anion (62a) which could conceivably yield dihydrocoumarin by the mechanism previously proposed. It is difficult to see how either dihydrocoumarin or melilotic acid could have arisen from the β-keto-ester or the ketone (61) itself.

The size of the heterocyclic ring was confirmed by Wolff-Kishner reduction of the ketone to the known homochroman (60).

(b) Cyclisation of the diester using sodium hydride in ether, at room temperature, was found not to go to completion. One of the products from the reaction was suspected of being the half-ester (74a) or (74b) arising from partial hydrolysis of the starting material. Although the i.r. spectrum showed absorptions attributable to both acid and ester functions it could not distinguish between the two possible half-esters. Hydrolysis of the material, however, did indeed produce dihydro-o-coumaroxyacetic acid.

The other product from the cyclisation was the required β-keto-ester (identical to that in (a)), obtained in only 15% yield. Hydrolysis of the β-keto-ester was in this instance carried out under acid catalysis, as was decarboxylation. The ketone (61) was obtained by this method in almost 11% yield overall.

(c) The most satisfactory method of cyclisation proved to be that using potassium-t-butoxide in dry benzene. In this case the reaction gave the required β-keto-ester in 66% yield and afforded only a small proportion of acidic material. The product from this cyclisation was much cleaner than that from (a) and (b).

An improved method for the production of the ketone (61) from the β-keto-ester was also found. Hydrolysis of the latter with methanolic potassium hydroxide readily gave the corresponding β-keto-acid in 73% yield. The acid, a low-melting solid, was observed to undergo spontaneous decarboxylation at room temperature. This was completed by heating the crude acid under reduced pressure. Prolonged heating during the decarboxylation was found to result in considerable polymerisation of the material.

It was also noted that the neutral material returned from the hydrolysis was not wholly unchanged starting material but appeared to contain a quantity of the ketone (61) presumably from decarboxylation of the β-keto-acid. Distillation of the product, however, did not effect any separation of β-keto-ester and the presumed ketone.

Homochroman-3-one was then treated with N-bromosuccinimide in dry carbon tetrachloride containing a trace of benzoyl peroxide. It was hoped that bromination would take place preferentially in the benzylic position and the bromo-ketone would then undergo elimination of hydrogen bromide to give the αβ-unsaturated ketone (75a). The latter, in its enol form (75b), being essentially a substituted benz-1-oxepin should give some indication of the properties of the oxepin ring system.

The ketone (61) was therefore treated under the bromination conditions described. The intermediate bromo-compound was not isolated but treated in the crude state with redistilled, dry collidine. A precipitate, presumed to be collidine-hydrobromide was readily obtained. The product from the reaction mixture, a yellow oil, was distilled, giving a pale oil which was observed to darken rapidly and become tarry in consistency. The i.r. spectrum of the distillate indicated that the product was most likely a mixture (ν max 1755, 1710, 1650 cm^{-1}).

A sample of the product on treatment with an acidic solution of 2:4-dinitrophenylhydrazine gave a brick-red precipitate which proved to be a mixture of compounds. The chief component of the mixture, a brick-red solid, was insoluble in most organic solvents with the exception of hot pyridine from which it could be deposited as an amorphous solid by addition of chloroform. No true analysis for the material could be obtained since a sample could not be satisfactorily recrystallised. Mass spectrometry however, indicated a parent ion at 538, corresponding to a possible molecular formula of $C_{22}H_{18}N_8O_9$. The second largest peak appeared at 341, i.e. a loss of 197, corresponding to $C_6H_5N_4O_4$.

The u.v. spectrum of the derivative gave some unusual results. In chloroform solution, the compound absorbed at λ max 255 mμ (log ϵ, 4.23), 395 mμ (log ϵ, 4.53) and 435 mμ (log ϵ, 4.47). In pyridine solution an intense purple colouration was obtained and the u.v. spectrum of this solution showed a continuous series of absorption peaks between 345 and 570 mμ in addition to another band at 312 mμ. On addition of one drop of water to the pyridine solution the purple colouration disappeared to leave a pale yellow solution.

One possible structure for the derivative is that of the hydrazide-hydrazone shown (76). This could have been formed either

(a) from the bromo-ketone (77) by normal hydrazone formation and elimination of hydrogen bromide between the molecule and a second molecule of reagent, or

(b) from the αβ-unsaturated ketone (75a) by normal hydrazone formation and addition of a second molecule of reagent across the double bond. Such a structure is in agreement with the mass-spectrometric results.

An alternative explanation is that bromination did not take place on the benzylic carbon atom, but on the carbon atom <u>α</u> to the ether function, to give the bromo-ketone (78). This cannot eliminate hydrogen bromide on treatment with base but on work-up of the reaction mixture could be hydrolysed to give the hemiacetal (79). This may be assumed to be readily opened to the corresponding hydroxy-aldehyde (80) which could form a <u>bis</u>-2:4-dinitrophenylhydrazone. This <u>bis</u>-derivative would also have a molecular weight of 538 and its insolubility would not be unexpected. Against this argument is the fact that the derivative showed no phenolic characteristics.

It was obvious that treatment of (61) with N-bromosuccinimide did not proceed in a straightforward manner to give the required $\alpha\beta$-unsaturated ketone. Even if the latter were present it appeared to be accompanied by other products in an unstable mixture.

Lack of success in preparing the unsaturated ketone (75a) led to a reconsideration of the potential uses of the β-keto-ester (72) itself. If the more probable isomer (72a) were converted to the corresponding enol-acetate (81a) it should be possible to insert into this molecule another double bond to give what again is essentially a substituted benz-1-oxepin (82). Apart from any information gained about the ring system from this compound, it should also be possible to hydrolyse both the ester and acetate groups to give the enol form (75b) of the ketone (61), already unsuccessfully sought by the route previously mentioned.

Several preparations of the enol-acetate were attempted. In the first instance, a solution of the β-keto-ester in dry pyridine was treated with acetyl chloride and allowed to stand at room temperature. Pronounced discolouration occurred but the product, after the usual work-up, on fractionation provided some material which gave a negative reaction with methanolic ferric chloride. The i.r. spectrum (carbon tetrachloride) showed some significant differences from the β-keto-ester, in the carbonyl region. The latter possessed three strong peaks, ν max 1743 cm^{-1} (normal ester), 1723 cm^{-1} (ring ketone) and 1650 cm^{-1} (chelated ester). The product from enol-acetylation showed more widely separated carbonyl bands at 1750 cm^{-1} and 1710 cm^{-1} while the band at 1650 cm^{-1} was reduced in intensity. The band at 1750 cm^{-1} may be attributed to the vinyl ester group and that at 1710 cm^{-1} to the other ester group, with the frequency lowered by conjugation to the double bond of the enol-acetate. Microanalysis of this compound was as expected for the desired enol-acetate (81a) or its possible isomer (81b).

Since (81) proved to be extremely labile, the preparation was modified by carrying out the reaction in an atmosphere of nitrogen and by avoiding the use of both acid and base during the work-up. These precautions, however, did not prevent marked deterioration in the product, and in no instance was a pure compound obtained although distillation did provide some enol-acetate uncontaminated by β-keto-ester.

In one attempted preparation of (81) using acetyl chloride and pyridine, anomalous results were observed. On distillation of the product, four fractions were obtained, the first having a boiling point noticeably lower than the other three. The i.r. spectrum of this fraction exhibited, in the carbonyl region, one main single sharp band at 1725 cm^{-1} and the whole spectrum was very similar to that of homochroman-3-one (61) itself. This fraction gave a slight positive reaction with methanolic ferric chloride. Both this and some characteristics of the i.r. spectrum indicated that the sample contained traces of β-keto-ester (72). The other fractions contained increasing amounts of β-keto-ester as well as the ketonic material. It is not difficult to explain the presence of the ketone (61) in the reaction mixture since hydrolysis and thermal decarboxylation of the β-keto-ester were already shown to give the ketone.

As confirmation of the presence of homochroman-3-one in the mixture, each fraction was treated with an acidic solution of 2:4-dinitrophenylhydrazine and from the chromatographed products there was isolated a crystalline yellow-orange solid, (m.p. 152-155°) whose m.p. was not depressed on admixture with a known sample of homochroman-3-one 2:4-dinitrophenylhydrazone. The later fractions gave less pure products.

As an alternative to the acetyl chloride - pyridine method of preparation, enol-acetylation was attempted using isopropenyl acetate. Although the 2:4-dinitrophenylhydrazone of acetone was isolated, indicating that the reagent had split into the necessary component parts for acetylation only β-keto-ester was obtained on work-up.

Despite the obvious lability of the enol-acetate, it was decided to use it for insertion of the last double bond into the required ring system. The presumed enol-acetate was treated in the usual way with N-bromosuccinimide in carbon tetrachloride. The intermediate bromo-compound was not isolated but refluxed in fresh solvent, during which evolution of hydrogen bromide was observed. The product, a pale yellow oil, gave a negative reaction with methanolic ferric chloride and was rapidly oxidised by aqueous alkaline permanganate. On distillation, however, an oil was obtained which gave a positive reaction with methanolic ferric chloride. The i.r. spectrum of this material did not correspond to either the starting enol-acetate or the β-keto-ester. The small amount of material available was not purified further but hydrolysed directly with methanolic potassium hydroxide. Hydrolysis appeared to be incomplete and some neutral starting material was returned. This was accompanied by an acidic material, a dark viscous oil which produced an intractable tar on attempted decarboxylation; no ketonic material could be isolated from this, although the product was treated with an acidic solution of 2:4-dinitrophenylhydrazine in the hope that an identifiable derivative might be obtained. The only product was an oily orange-red precipitate which could not be purified.

In view of the lability of the enol-acetate and unsuccessful decarboxylation of the final product (83) it was decided to abandon this line of approach to benz-1-oxepin.

It was felt, however, that some of the difficulty experienced in working with the β-keto-ester might have been due to the fact that both of the possible isomers (72a) and (72b) were present and that some further investigation was necessary. The β-keto-ester itself, on standing, was observed to become slightly cloudy but it could not be induced to crystallise, nor was any solid separated by trituration. On distillation, no fractionation of isomers took place.

Preparation of the 2:4-dinitrophenylhydrazone(s) gave a yellow solid contaminated with a brown oily solid. Chromatography of the product on bentonite-kieselguhr (4:1) yielded only a low-melting solid of indefinite m.p. which could not be characterised.

The n.m.r. spectrum was recorded but proved uninformative. If both possible isomers were present, each of which could exist in an enol as well as a keto form, there would be four different species contributing to the spectrum. The results obtained were not consistent with what would be expected for any one of the species. The spectrum was of poor resolution and no integration was possible. G.l.c. was hardly more informative (see Experimental).

Route B.

The key intermediate in this route, as already stated was homochroman-5-one (65). The starting material for the preparation of this ketone was γ-phenoxybutyric acid whose preparation has been recorded in the literature. Dann and Arndt[66] prepared it from condensation of phenol with bromocrotonic ester, followed by reduction, but the overall yield was only 30%. An improved method was that due to Reppe[67], in which the acid was prepared in 76% yield by heating equimolar quantities of sodium phenolate and γ-butyrolactone at 200°. In our case, the acid was obtained in 90% yield by a slight modification of Reppe's method.

Cyclisation of the acid (84) had already been reported by several workers. Powell and Anderson[68] achieved only partial success in their attempted cyclisation even when no greater than 1g quantities were used; indeed, they did not isolate the required ketone (65), but identified it as its oxime and semicarbazone. Dann and Arndt carried out the cyclisation using both syrupy phosphoric acid and hydrogen fluoride. Although they reported better yields with the latter, the working conditions were not at all practicable. Subsequent work has shown that a mixture of phosphorus pentoxide and 85% orthophosphoric acid as cyclisation agent gives cleaner products and higher yields than commercial syrupy phosphoric acid itself. This improved method was therefore chosen.

On the first attempt, a mixture of products was obtained, consisting of 92% neutral material and 8% acidic material. The neutral material on distillation gave pure homochroman-5-one (65) in 75% yield overall. The nature of the acidic material is discussed in Appendix I (p.77). In a subsequent preparation yet another by-product was obtained (vide also Appendix I).

The ketone (65) was readily reduced (Wolff-Kishner) to (60), and gave an orange 2:4-dinitrophenylhydrazone (λ max 217-248, 370 mμ).

Of the several possible uses for this ketone, the one first considered was its conversion into the α-bromo-ketone (85) which by dehydrobromination should give the $\alpha\beta$-unsaturated ketone (86). Enolisation of (86) theoretically would give a substituted benz-1-oxepin, while reduction and dehydration could conceivably give (3; X = O) itself.

This scheme was baulked at the outset when it was found that the bromo-ketone could not be satisfactorily prepared. Anhydrous conditions were employed so that bromination should take place in the side-chain and not in the nucleus. The initial product was shown to be a mixture of starting ketone and α-bromo-ketone. The i.r. spectrum possessed two carbonyl absorption bands, ν max 1695 cm^{-1} (bromo-ketone), 1680 cm^{-1} (normal aryl ketone) . Although the calculated amount of bromine had already been taken up, the crude product was treated with a fresh portion of bromine. No further uptake was, however, observed. Repeated attempts at bromination always resulted in a partially brominated product. The bromo-ketone (85) could not be separated from the starting material by distillation but its presence in the mixture was confirmed by treatment of the product with o-phenylenediamine. A crystalline quinoxaline derivative was isolated.

The expected structure of the fully-oxidised quinoxaline would be as shown (87), but it is not impossible that a dihydroquinoxaline (88) or even a tetrahydroquinoxaline (89) could be obtained. It was also possible that the solid isolated was merely a derivative of homochroman-5-one present in the mixture. This would be the amine (90). Since these possible structures differed from each other only by two or four hydrogen atoms, microanalysis was not sufficiently accurate to differentiate amongst them. Mass-spectrometric evidence, however, indicated the fully oxidised derivative (87) as the most likely structure, since a parent peak was obtained at mass 248. ($C_{16}H_{12}N_2O^+$). The derivative showed λ max 244 mμ (log ϵ, 4.41) and 330 mμ (log ϵ, 3.98).

Utilisation of the ketone (65) via the α-bromo compound was abandoned. Attention was then turned to production of the olefin, 2:3-dihydrobenz-1-oxepin (91) from homochroman-5-one. Decomposition of the p-toluenesulphonylhydrazone was first considered. It is known[69] that decomposition of such derivatives can lead to olefins (the Bamford-Stevens reaction).

The crystalline derivative was readily obtained in 81% yield and treated with a standard (1 N) solution of sodium ethyleneglycollate. The product was separated into acidic and neutral fractions. The former was a solid (m.p. 84°) and was shown (i.r. and m.p.) to be the water-insoluble p-toluene-sulphinic acid. The yield of acid was 73% of that theoretically expected from decomposition and indicated that degeneration of the p-toluenesulphonylhydrazone had taken place at least to the stage of the intermediate diazo compound.

The neutral material recovered from the reaction possessed a pronounced phenolic odour, gave a green colouration with methanolic ferric chloride and was partially soluble in aqueous sodium hydroxide. Apart from end-absorption, the the u.v. spectrum showed λ max at 268 and 308 mμ . The i.r.

spectrum showed hydroxyl absorption. This neutral material was cloudy in appearance and because of its partial solubility in aqueous base, was suspected of being a mixture. It was therefore separated by basic extraction into neutral and base-soluble components. The latter (8% of the total) was an orange-coloured viscous oil with a pronounced phenolic odour, giving a green colouration with methanolic ferric chloride. The u.v. spectrum had λ max. 266 and 308 mμ. Lack of material and its impurity prevented identification of this phenol. The presumed neutral portion (92%) from the extraction was a yellow-green liquid, showing hydroxyl absorption in the i.r., but possessing now λ max at 268 mμ only. Distillation of the liquid, however, appeared to occasion some changes in it. Four fractions were collected, the first two being separated from the latter two by a difference of approximately 20° in boiling point. The middle two fractions were observed to undergo distinct colour changes on heating and cooling.

The lower-boiling portion of the distillate possessed a phenolic odour and was similar in character to the phenol already examined. (The u.v. spectrum now showed λ max. 265 and 308 mμ; since the latter absorption was not present in the undistilled material it suggested that it had been produced on heating). The higher-boiling fractions of the distillate, virtually odourless oils, giving negative reactions with methanolic ferric chloride, showed λ max 269-270 mμ only. The i.r. spectrum showed increased intensity of the aromatic bands and a very sharp band at 1620 cm^{-1}, but no absorption at lower frequency attributable to a cis double bond. There was also very strong hydroxyl absorption (3500-3400 cm^{-1}), not of the usual broad type expected of a phenol, in the liquid state. In view of the mixtures obtained and the difficulty experienced in getting any component freed from the mixture, this line was not investigated further. It is possible that some of the required olefin (91) was present in the mixture (as a comparison of i.r. spectra later indicated, when a sample of pure olefin was available) but it was not positively identified at this time.

An alternative method for obtaining the required olefin (91), via dehydration of homochroman-5-ol (92) was explored. The alcohol was readily obtained (98% yield) from the corresponding ketone (65) by reduction with sodium borohydride. The alcohol, a crystalline solid, showed evidence of intramolecular hydrogen bonding in the solid state. In its i.r. spectrum, the normal alcohol absorption (λ max 3200 cm^{-1}) was accompanied by a weaker band at 2600 cm^{-1}. This presumably could be that due to an internally bonded structure such as (93).

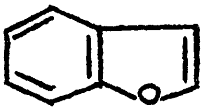
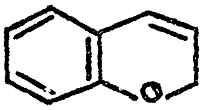
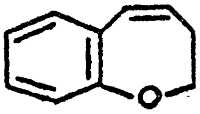
Dehydration of the alcohol was successfully achieved by two methods. Treatment with boric acid gave the olefin (91) in 95% yield, while dehydration of the alcohol in methanol containing concentrated hydrochloric acid gave the same olefin in 83% yield. The olefin, a colourless low-boiling liquid, rapidly decolourised alkaline permanganate and gave an orange colour instantaneously with tetranitromethane. The i.r. spectrum showed enhanced intensity of the aromatic absorption bands, a band at 1625 cm^{-1} and two new bands at 700 and 660 cm^{-1}, indicating the presence of a phenyl-conjugated double bond.

The structure of the olefin, however, was rigorously investigated to ensure that no skeletal change (e.g. ring contraction) or double bond shift had taken place during dehydration.

On catalytic reduction the compound gave the known homochroman (60) with uptake of one molar equivalent of hydrogen, confirming both ring size and presence of one double bond.

The n.m.r. spectrum of the olefin (94) showed the following signals:- multiplet at 3.0 τ assignable to aromatic protons; double triplet centred at 3.7τ, arising from H_a, split by coupling with H_b (J_{ab} = 12 cps), each half of this doublet further split by long-range coupling with $H_{c,d}$ ($J_{ac} = J_{ad}$ = 1.9 cps); a similar double triplet centred at

TABLE I

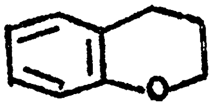
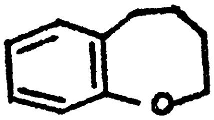
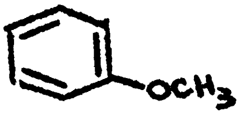
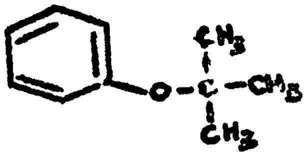
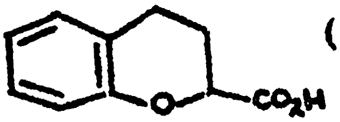
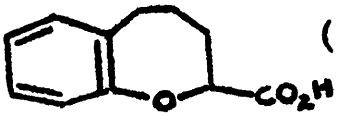
Compound		λ_{max}(mμ)	ε	Ref.
	(96)	245 275 282	(10,000) (2,512) (2,239)	75
	(97)	263	(4,266)	76
	(91)	255 293	(10,000) (1,622)	—

4.3τ, assigned to H_b, split by coupling with H_a (J_{ab} = 12 cps) to a doublet and further split by coupling with $H_{c,d}$ (J_{bc} = J_{bd} = 4.8 cps); triplet centred at 5.9τ, assigned to $H_{e,f}$ split by coupling with $H_{c,d}$ (J_{ce} = 4.8 cps); an octet centred at 7.56τ assigned to the allylic protons $H_{c,d}$ split to a triplet by coupling with $H_{e,f}$, further split by coupling with H_b, resulting in a quartet, and finally split to an octet by coupling with H_a (J_{ac} = J_{ad} = 1.9 cps).

The u.v. spectrum of the olefin proved to be of some interest. The compound absorbed at λ max 255 and 293 mμ (ϵ, 10,000 and 1,622 respectively). These values were compared with those for benzfuran (96) and for 3:4-chromene (97), and at first sight appeared to be discrepant (Table I). An examination of the u.v. spectra of related compounds was therefore made.

In conjunction with changes in ring size in the series under discussion, there are two factors to be considered - the effect of ring size on the ether group and also on the double bond in the heterocyclic ring. Several workers[70-74] have studied the first of these factors and been able to rationalise changes both in chemical reactivity of the ether group (e.g. basicity) and in absorption spectra. Baddeley[72] postulated an increase of steric interaction with decrease of the oxygen - interplanar angle of the ether group and the benzene ring in aromatic ethers. In the system (95),

TABLE II

Compound		λ_{max}(mμ)	ε	Ref.
	(98)	275 282	(3,162)	77
	(99)	274 279	(1,622)	78
	(60)	266–267 269–270	(668) (620)	—
	(100)	265 272 278	(1,259) (1,995) (1,778)	71
	(101)	(259) 264 270		71
	(102)	274 281	(1,800) (1,860)	73
	(103)	265 270	(570) (555)	73

conjugation should be a maximum when n = 5 and should decrease with increase in the value of n, in so far as this increase rotates the —OCH_2 bond away from the plane of the benzene ring.

In the series shown (Table II) the steady decrease in λ max (98) → (99) → (60) as the heterocyclic ring is enlarged is explained by increased puckering of the heterocyclic ring, forcing C_2 out of the plane of the benzene ring, thereby decreasing the interaction between the unshared pairs of electrons on the oxygen atom and the aromatic ring. The values for these compounds may, in turn, be compared with those for anisole (100) and for t-butylphenyl ether (101). In anisole, a contribution from an ionic structure is possible, whereas it is not in the ether (101) whose spectrum is nearly identical with that of homochroman (60). This argument may be substantiated by a comparison of the absorption spectra of the acids (102) and (103).

The second factor is the possibility of changes in the absorption of a styrene-like double bond. In styrenes the main absorption band appears in the region of 248 mμ, with additional characteristic bands λ max 282, 291 mμ which are due to displaced benzenoid absorption. The 248 mμ band is sensitive to changes in conformational environment and its intensity and position are susceptible to loss of coplanarity.

TABLE III

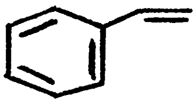
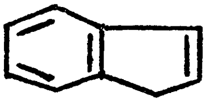
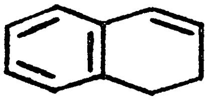
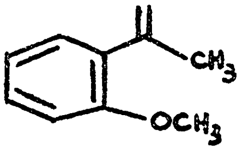
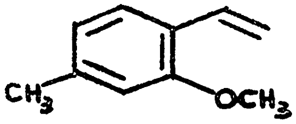
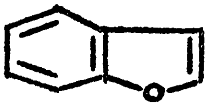
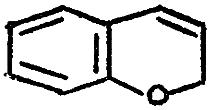
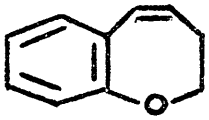
Compound		λ_{max}(mμ)	ε	Ref.
	(104)	248 282 291	(14,000) (750) (500)	79
	(105)	249 280 290	(11,000) (450) (750)	80
	(106)	262 292	(10,500) (700)	80

TABLE IV

Compound		λ_{max}(mμ)	ε	Ref.
	(108)	274 281	(1,995) (1,585)	81
	(109)	250	(11,500)	82
	(96)	245 275 282	(10,000) (2,512) (2,239)	75
	(97)	263	(4,266)	76
	(91)	255 293	(10,000) (1,622)	—

The absorption of indene (105) (Table III) is very similar to that of styrene (104) itself, while 1:2-dihydronaphthalene (106) shows a shift of the main band to longer wave-lengths and some reduction in intensity. Unfortunately no data appears to be available for the homologue (107).

In the series being considered (Table I) both of these factors will be operating; from the limited data available it would appear that the effect of ring size on the ether linkage is greater than the corresponding effect on styrene absorption. In the open-chain compounds containing both an ether and a double bond (Table IV), (108) shows predominantly anisole-like absorption whereas the compound (109) is more styrene-like. Of the cyclised compounds of this type, benzfuran (96) reflects a high degree of conjugation in its absorption pattern. In 3:4-chromene (97), considerably reduced intensity of the main styrene-like band is observed. This may be attributed to the fact that the presence of the ether oxygen atom in the heterocyclic ring forces the double bond out of the plane of the benzene ring thereby reducing conjugation. In the olefin (91) however, it would appear that while the oxygen atom may still be out of the plane of the aromatic ring, the greater size of the heterocyclic ring allows the double bond to become more nearly coplanar with the benzene ring than the corresponding six-membered ring does.

It was observed that on standing for some time samples of the olefin showed signs of deterioration. This was later investigated (See Appendix II, p. 83).

The αβ-unsaturated ketone (75) previously sought (p.41) should be obtainable by allylic oxidation of the olefin. It is known that, in general, activated methyl or methylene groups may be oxidised by selenium dioxide. If activated by a carbonyl group, the product is usually an aldehyde or ketone (from methyl and methylene respectively); if the activating group is a double or a triple bond, the product is generally the corresponding unsaturated alcohol. It has further been noted that a methyl or methylene group adjacent to one or more aromatic rings may also be converted into the corresponding carbonyl group. Some olefins, in addition, are known to undergo loss of hydrogen and addition of oxygen to give α-diketones.

In our case therefore, one might anticipate that the most likely product would be the allylic alcohol (110; R = H) although conjugation with the benzene ring could conceivably activate the allylic methylene sufficiently to give some ketonic material. Whether any oxidation at the double bond itself would take place or not is a matter for some speculation. The possibility of obtaining either the alcohol or the ketone or a mixture of both was no deterrent to this route since not only are both potentially useful, but are theoretically readily interconvertible. It is known that acetic acid and acetic anhydride, if used as solvents for the reaction[83] can combine with the required product, but this provides the advantage of being able to isolate any alcohol present as its acetate.

Acetic anhydride was chosen as a suitable solvent since it is less likely to give a mixture of alcohol and acetate.

At the first attempt a molar ratio (olefin : selenium dioxide) of 2:1 was used to minimise the extent of oxidation at the allylic position, and the reaction was carried out for 2 hours in acetic anhydride. The crude product, a brown oil, was shown to contain traces of acetic anhydride, which was removed by distillation. The required acetate (110; R = $COCH_3$) distilled as a yellow oil; it was observed that the tarry residue from distillation contained hydroxyl absorption bands in its i.r. spectrum. The yield of acetate in this experiment was only 25%, but a modification of the method improved this yield. Reduction of the reaction time to 1.5 hours, coupled with the use of acetic acid as solvent rather than acetic anhydride, raised the yield to 83%. Reaction times of less than 1.5 hours resulted in an increase in the amount of unchanged olefin and reduction of the yield of acetate to 62%. In subsequent preparations, the crude product from the oxidation was treated with a mixture of acetic anhydride in pyridine to ensure complete conversion into the acetate.

The i.r. spectrum of the acetate showed the normal expected ester absorption bands. The n.m.r. spectrum was ill-defined but gave signals at 2.9τ(aromatics), 3.5τ (doublet, assigned to proton on C_5), 4.0τ(multiplet, assigned to proton on C_4), 4.42τ(quartet, assigned to allylic proton on C_3), 5.75τ(doublet, assigned to protons on C_2) and 7.9τ(singlet, assigned to methyl protons).

It was noted that samples of the acetate even when redistilled, if allowed to stand at room temperature for some time, deposited a crystalline material. This was removed and examined separately (See Appendix III, p.85).

Hydrolysis of the acetate was carried out under both acidic and basic catalysis. With acid hydrolysis, some unchanged acetate was always left but the product was much cleaner than that obtained by base hydrolysis. Under base catalysis (alcohol/potassium hydroxide) hydrolysis proceeded smoothly to give a liquid alcohol (66% yield) which was shown to be the required compound (110; R = H). This alcohol was accompanied by a white crystalline solid which could be separated from the required compound by precipitation with ether. The solid was removed and examined separately.

(The nature of, and possible structure for this material are discussed in Appendix III, p.86).

The structure of the liquid alcohol was confirmed by its physical data. The i.r. spectrum contained a striking example of the effect of conjugation of a double bond with an aromatic ring. Four strong bands appeared in the region 1600 - 1480 cm^{-1}:- νmax 1630 cm^{-1} (phenyl conjugated double bond), and 1603, 1582, 1492 cm^{-1} (aromatics). Strong hydroxyl absorption was also present, νmax 3300 cm^{-1}. The u.v. spectrum confirmed the conjugation of the double bond with the aromatic ring, showing that hydrolysis had not occasioned any double bond shift; λ max 255 mμ (log ϵ, 3.92), 290 mμ (log ϵ, 3.18) .

The alcohol was found to deteriorate on standing for a few weeks at room temperature. From i.r. spectra it was found that carbonyl functions developed at the expense of the conjugated double bond system, a marked reduction in the intensity of the double bond and conjugated aromatic bands being observed. A reduction in intensity of hydroxyl absorption was also noted. The carbonyl bands were broad and somewhat indistinct but appeared both in the regions of 1720 and 1680 cm^{-1}. Distillation of old samples of alcohol did not effect a separation of any ketonic compounds from hydroxylic ones. The presence of a mixture was confirmed by attempted preparation of 2:4-dinitrophenylhydrazones of any ketonic products present. Although an orange solid was obtained, chromatography of this failed to separate an obvious mixture into any recognisable components.

Storage of the alcohol under nitrogen slowed up but did not prevent oxidation so that the alcohol had to be freshly prepared from the corresponding acetate each time it was required.

Oxidation of the allylic alcohol (110; R = H) to the required ketone (75) was initially attempted using manganese dioxide. A small scale test experiment was carried out in carbon tetrachloride using a commercial grade manganese dioxide. The reaction was carried out at room temperature for 7 hours and yielded a small quantity of a colourless oil which solidified on cooling, to fine white needles, m.p. 60-65°. The i.r. spectrum showed that this was not the expected ketone, although it may have been present (ν max 1740 (m), 1700(s), 1680 (sh;m) cm^{-1}). The attempted preparation of a 2:4-dinitrophenylhydrazone gave initially a soluble product. Concentration of the solution gave only an oil which could not be induced to crystallise. Since lack of material precluded identification of the oxidation product, the experiment was repeated on a larger scale, but it was disturbing to find that the solid product was never again obtained even under the same conditions. From the bulk oxidation there was obtained an oil which would not solidify. The i.r. spectrum of the oil differed from that of the first solid product and indicated a possible mixture. Distillation effected only a slight separation of components. Two fractions were obtained, with dissimilar i.r. spectra. The lower boiling fraction appeared to be a mixture of ketonic and olefinic materials (ν max 1730(s), 1660(s), 1600(s), 1570(s), 1480(s), 710(s), 670(s) cm^{-1}). The higher boiling fraction also contained ketonic material, differing from that of the first fraction (ν max 1750(w), 1730(s), 1660(s), 1600(s), 1570(s), 1480(s), 710(s), 670(s) cm^{-1}).

Attempted preparation of a 2:4-dinitrophenylhydrazone from the first fraction gave initially an orange precipitate, and on standing, a deep red deposit. The mixture could not be properly recrystallised and no definite m.p. was obtained for the material. The second fraction, however, yielded an orange-red solid of low solubility which appeared to be one compound (m.p. 175°).

When the oxidation was carried out for longer periods of time, an oil was obtained whose i.r. spectrum showed no hydroxyl absorption but possessed a complex carbonyl region. The product was presumed to be a mixture although on chromatography of the precipitate obtained with 2:4-dinitrophenylhydrazine solution, the main product isolated was identical with that previously obtained (m.p. 175°) (λ max 250, 390 mμ; cf. homochroman-3-one, 2:4-dinitrophenylhydrazone — λ max 261, 354 mμ).

Although the oxidation products were obviously mixtures it was hoped that after reduction, it would be possible to identify any homochroman-3-one present. The reduction was carried out over 5% palladium - charcoal as catalyst, stopping the reaction when one molar equivalent of hydrogen had been taken up. The product, a yellow oil, showed νmax 3500, 1730(s) cm^{-1} and weak double bond absorption. Further reduction of the saturated ketone (61) to the corresponding alcohol may have taken place. The mixture was treated with 2:4-dinitrophenylhydrazine and (61) identified as its derivative, a yellow crystalline solid, m.p. 158-159°. The 2:4-dinitrophenylhydrazone of a known sample of (61) had m.p. 160-161°. On admixture of the two samples, the m.p. was not depressed.

From these results, it may be concluded that the required unsaturated ketone (75) was present in the mixture of products from oxidation of the allylic alcohol. This, however, could not be isolated in a pure state. (Later work, using the newly-introduced technique of t.l.c., did in fact show that oxidation of freshly-prepared alcohol by manganese dioxide gave four products. The R_f values of these compounds were close together and did not favour separation by chromatography. Likewise, t.l.c. of a mixture of the corresponding 2:4-dinitrophenylhydrazones indicated that chromatographic separation would be impracticable).

Lack of reproducible results and inhomogeneity of the product caused oxidation by this method to be discarded as unhelpful. An alternative reagent tried was chromium trioxide in sulphuric acid (Jones's reagent)[84]. Treatment of the alcohol with Jones's reagent gave a product (in 40% yield) consisting of a yellow oil containing some solid. T.l.c. of the product showed it to be a mixture of four compounds, three of which were shown, by use of appropriate staining agents, to contain carbonyl functions, while the fourth (present in only small amounts) was identified as the olefin (91); this presumably was carried over from preparation of the alcohol. Trituration of the product with ether precipitated out a solid which was removed and purified by sublimation The high-melting solid gave a yellow 2:4-dinitrophenylhydrazone and showed two carbonyl bands in the i.r. spectrum (1700 and 1680 cm^{-1}). Weak hydroxylic absorption of the acidic type was also present, and accompanied by an unusual benzene substitution pattern. Lack of material, however, precluded any further investigation.

The residual oxidation product after removal of this solid was chromatographed, but a successful separation of the components of the mixture was not achieved. Spectroscopic evidence, however, did give some indication of the nature of the components. The first fractions were olefinic in character and were followed by ketonic material similar to that obtained by manganese dioxide oxidation. This material appeared to be predominantly the required ketone (75) (νmax 1660 cm^{-1}). Later fractions were more impure and contained some of the same solid which could be precipitated by addition of ether to the reaction mixture.

A sample of the crude ketone (75) was catalytically reduced, stopping the reaction when one molar equivalent of hydrogen had been taken up. The product, a yellow oil, on spectroscopic evidence, was a mixture of saturated and unsaturated ketones. Chromatography of the mixed 2:4-dinitrophenylhydrazones on bentonite-kieselguhr proved ineffective as a means of complete separation, but it was possible to isolate from the column a fraction which was further purified by repeated crystallisations. The orange needles (m.p. 155-159°) did not depress the m.p. of homochroman-3-one, 2:4-dinitrophenylhydrazone.

As in the case of the manganese dioxide oxidations, therefore, the required ketone appeared to be present, but accompanied by other oxidation products from which it could not easily be separated. Although every effort was made to free the alcohol (110; R = H) from the "diol" impurity (see p.86) it is not impossible that traces of it remained. Oxidation of this "diol" would add further complications to the mixture already obtained from the mono-ol.

The sample of $\alpha\beta$-unsaturated ketone (75) obtained by chromatography was examined for enolisation. The u.v. absorption of the material was recorded in both neutral and basic solution, but no shift in λ max was observed, indicating that the ketone was not readily enolisable to the substituted benz-1-oxepin system (75b) hoped for.

In view of the difficulty experienced in obtaining the ketone (75) and its apparent non-enolisation this line of approach was not investigated further. Had it been possible to obtain the required ketone (75) in a pure state and in reasonable yield, one way of introducing the necessary third double bond in the heterocyclic ring would have been by pyrolysis of the amine oxide (111), obtainable theoretically from the ketone via its enamine.

Seeking an alternative method of introduction of the required double bond, attention was turned once again to the allylic acetate (110; R = $COCH_3$). It is known that pyrolysis of acetates, amongst other esters, can yield olefins[85], and this was therefore attempted. The pyrolysis was carried out initially at 380°, under reduced pressure and in a nitrogenous atmosphere, collecting the pyrolysate in a vessel cooled by liquid nitrogen. A yellow oil was collected and proved to be unchanged acetate. Elevation of the temperature to 450° failed to pyrolyse the acetate which again distilled over unchanged. Failure could, in part, be attributed to the fact that the acetate was very difficult to vaporize, only a small portion of the starting material passing through the pyrolysis chamber. In view of this, the corresponding tosylate (110; R = Ts) and carbonate (110; R = $CO_2C_2H_5$) were considered as potentially useful for the same purpose.

Attempts were made to prepare the tosylate in the usual way, using p-toluenesulphonyl chloride in pyridine. The product consisted mainly of unreacted reagent but the residue after removal of this was shown to be a mixture of five compounds. Repetition of the procedure with a longer reaction time gave a small amount of an unidentified yellow oil, whose i.r. spectrum did, however, exhibit the expected tosylate bands; it was found to be a mixture of three components. Although no pure tosylate was isolated the mixture was subjected to treatment with refluxing collidine. The recovered material proved to be only unreacted starting material. Treatment with quinoline gave the same result. Since it was considered possible that the alcohol could be reacting with pyridine itself to give some of the compounds found in the reaction, a sample of pure alcohol (110; R = H) was allowed to stand at room temperature in pyridine for 24 hours. No reaction was observed to have taken place and the alcohol was recovered unchanged. The compounds produced on attempted tosylation have not so far been identified and this part of the work was abandoned.

Since it has been found that pyrolysis of carbonates to olefins generally proceeds at a lower temperature than that required for the corresponding acetates, and in addition, that most carbonates are readily formed, it was hoped that better results would be obtained from this particular ester.

On a small pilot run, a sample of freshly-prepared, redistilled alcohol (110; R = H) was treated with ethyl chloroformate to give an oil with an ester-like odour. (ν max 1740, 1250 cm^{-1}; hydroxyl absorption absent). Since this initial reaction was carried out on a small scale the supposed carbonate was not purified first but was pyrolysed in the crude state. The pyrolysis was carried out in diethyl phthalate at 220° and the reaction product separated into neutral and base-soluble materials. It was anticipated that benz-1-oxepin (3; X = O), if produced in the reaction, might undergo ring collapse at the temperature of the pyrolysis to give a phenol. The base-soluble portion of the product was therefore examined particularly for the presence of any phenolic material. This fraction, a very small amount of a brown oil, did have a phenolic odour. The i.r. spectrum, although indistinct, did not correspond to that of α-naphthol, one of the possible products of ring collapse. The product did not give any colouration with methanolic ferric chloride but some phenols (one of them being α-naphthol) are known not to give characteristic colour reactions. On coupling with a diazo salt, a red azo-dye was obtained. Lack of material and the impurity of what little there was has so far prevented identification of this phenol.

Encouraged, however, by the presence of some phenolic material in the product, the reaction was attempted on a larger scale. The alcohol (110; R = H) was treated exactly as before with ethyl/chloroformate in pyridine to yield the expected yellow oil which was this time distilled, and the product analysed. Rather unexpectedly, the analysis figures did not correspond to those required for the carbonate (110; $R = CO_2C_2H_5$), but were more nearly (but not quite) in agreement with those expected for the αβ-unsaturated ketone (75). The i.r. spectrum of the distilled material showed slight differences from that of the crude product. The carbonyl band was sharper than might be expected for a carbonate, which is generally reported as being a broad absorption. The position of the band remained the same, but this, in turn, was not in accordance with that expected for an $\alpha\beta$-unsaturated ketone.

Other properties of the oil gave apparently anomalous results. A precipitate was readily obtained with an acidic solution of 2:4-dinitrophenylhydrazine but was subsequently shown to be a mixture. The oil was soluble in aqueous sodium hydroxide yet showed no shift in its u.v. absorption spectrum in basic solution. The oil was shown by t.l.c. to consist of one major product and this did in fact correspond to one of the products obtained on oxidation of the alcohol (110; R = H) with manganese dioxide (see p.64).

The supposed "carbonate" was subjected to hydrolysis under basic catalysis and the product separated into neutral and base-soluble fractions. The neutral fraction, a red oil, which turned bright green on standing overnight, gave no colouration with ferric chloride solution, only a slight precipitate with 2:4-dinitrophenylhydrazine and was shown by t.l.c. to contain eight different compounds. The base-soluble fraction was a yellow oil which turned dark red on standing and was found to contain six compounds. In view of the mixture of products obtained, investigation into the nature of the "carbonate" by hydrolysis was abandoned.

Permanganate oxidation of the "carbonate" likewise gave a mixture of products. The structure of the "carbonate" remains as yet undetermined and further evidence, which lack of time did not permit, would be necessary for the elucidation.

The reason for the failure of the alcohol to form both a normal tosylate and a carbonate, but not an acetate, remains as yet unknown. Since all these reactions were carried out in pyridine and the alcohol itself was shown not to react with pyridine, the use of this particular solvent itself cannot be the answer.

One other possible method of introducing the last double bond into the required ring system still remained. This consisted of treating the olefin (91) with N-bromosuccinimide to give the allylic bromide (112) which could be dehydrobrominated to benz-1-oxepin itself or to a product of ring collapse of the latter. Failure of previous work to give even a substituted benz-1-oxepin meant that it was not possible to gauge the stability or otherwise of the required ring system, and it was felt that the parent compound itself might not be readily obtainable. The presence of a product of ring collapse of (3; X = O) from the bromination-dehydrobromination reaction would at least indicate, however, that benz-1-oxepin had existed however transiently.

On treatment of the olefin, in carbon tetrachloride, with N-bromosuccinimide containing a trace of benzoyl peroxide, succinimide was produced slowly as bromination appeared to take place. The crude product was not isolated but treated directly with collidine in carbon tetrachloride. A very slight precipitate was immediately obtained but heating produced a dark insoluble oil. On work-up, the product was a pale yellow oil which was chromatographed. Six different fractions were obtained, the first one, eluted with light petroleum, being the most interesting. This oil, which possessed a pronounced olefinic odour, had an i.r. spectrum which did not correspond exactly to that of the starting olefin.* The band at 1620 cm^{-1} was of much greater intensity than the corresponding band observed in the olefin and the two strong bands at 700 and 660 cm^{-1} present in the

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* Following his successful synthesis of benz-1-oxepin (3; X=O), Professor Sondheimer most kindly forwarded a copy of its i.r. spectrum for comparative purposes. On the basis of spectral evidence alone it was concluded that while the material obtained from chromatography in our case was not (3; X = O) itself, the possibility that it was present in a mixture of olefinic materials could not be ruled out.

spectrum of the olefin were completely absent in this case. The region 1300-900 cm^{-1} also contained some differences. The material failed to give an adduct with maleic anhydride; this only indicated that were benz-1-oxepin present in this fraction, it did not behave as a diene. On standing, the oil darkened rapidly and became more viscous.

The i.r. spectrum of the second fraction from chromatography indicated that it was a mixture of the unknown olefinic product and the starting material (91). Subsequent fractions were found from their i.r. spectra to contain hydroxyl and carbonyl functions. Although these compounds could not be identified because of the mixture present, spectral evidence indicated that one of the compounds present could be the allylic alcohol (110; R = H). Since the i.r. spectrum of the crude material before chromatography showed no hydroxyl absorption, this presumably could have arisen from hydrolysis on the column of the corresponding bromide (112). The carbonyl compounds were not present in sufficient quantity to identify them by means of their 2:4-dinitrophenylhydrazones.

One may conclude that while some interesting results were obtained, the attempted synthesis of benz-1-oxepin by the routes described was severely hampered by production of by-products and by deterioration of intermediates. Were it possible to separate rigorously the mixtures obtained at each stage and to isolate the required compounds in reasonable yield, the desired synthesis might still be achieved. This would, however, have taken much more time than was available for this work.

Appendix I.

By-products from cyclisation of γ-phenoxybutyric acid (84) to homochroman-5-one (65).

The fact that two different by-products were obtained in the course of this reaction (p. 50) was not at all surprising.

Dann and Arndt[66] found that, in general, treatment of γ-aryloxybutyric acids with anhydrous hydrogen fluoride or polyphosphoric acid gave good yields of homochromanones when the para position was blocked; otherwise para-polymeric condensation products predominated. These workers, in fact, attempted to cyclise γ-phenoxybutyric acid itself using both reagents. With syrupy phosphoric acid they obtained the ketone (65) in 36% yield (but make no mention of by-products) while by the hydrogen fluoride method only polymeric materials were obtained. One of these was reported as a highly insoluble solid, m.p. 250°, to which they attributed the structure (113) where the value of n was unspecified.

Neither of the by-products isolated in this present work corresponded to the high-melting solid (113) mentioned by Dann and Arndt. The reaction was however carried out under the agency of a mixture of phosphorus pentoxide and 85% orthophosphoric acid and not exactly under the conditions used by Dann and Arndt.

By-product 1.

In each cyclisation product there was always present (to the extent of approximately 8% of the total), an acidic compound, removed from the reaction mixture in aqueous sodium carbonate. The substance was a white crystalline solid, sparingly soluble in most organic solvents, but recrystallisable from water as needles, m.p. 141-142°. Drying at 100° under reduced pressure appeared to cause decomposition. The solid was soluble in aqueous sodium carbonate and could be reprecipitated by the addition of acid. It gave no colouration with methanolic ferric chloride. On treatment with acidic 2:4-dinitrophenylhydrazine a crimson precipitate was obtained, m.p. 112-116°. This derivative appeared to be still acidic, being soluble in aqueous alkalis (ammonium hydroxide, sodium hydroxide and sodium carbonate). This suggested that the compound might be a keto-acid.

Microanalysis of the solid showed that the compound contained no phosphorous and that the empirical formula was $C_{10}H_{12}O_3$. On this basis it was at first thought that the compound could be a linear condensation product present as a hydrate, i.e. of formula $(C_{10}H_{12}O_3)_2$ with a possible structure as shown (114). Such a structure would account for decomposition on drying and for the obtention of an acidic 2:4-dinitrophenylhydrazone. Mass-spectrometric evidence however, eliminated this possibility, for a parent ion was obtained of mass 180, corresponding to a molecular formula of $C_{10}H_{12}O_3$. The compound showed ready loss of water to give the second largest peak at mass 162. The compound therefore had the same mass (180) as the starting material, γ-phenoxybutyric acid. Although the compound was not the acid (84) itself, it was possible that it was its dimer which, during mass-spectrometry merely split into two molecules, giving the same parent ion. This theory was rejected on comparison of the cracking pattern of the unknown acid with that of an authentic sample of γ-phenoxybutyric acid. More conclusive proof would have been obtained by esterification of the unknown acid but extreme insolubility prohibited this.

The unknown compound possessed an unusual i.r. spectrum. No solution spectra were possible due to solubility difficulties but an i.r. spectrum was recorded from a potassium chloride disc. The compound showed νmax 3350(s), 3070(s), 1650(vs), 1600 (m), 1580(vs), 1505(m), 1474(m), 1376(s), 1316(s), 1294(s), 1260(m), 1220(m), 1180(m), 1060(m), 1020(m), 847(s), 760-740(m) cm^{-1}. The band at 3350 cm^{-1} was extremely sharp and narrow. Although, in nujol, some weak broad hydroxylic absorption of the acidic type was observed, in the carbonyl region only the single band at 1650 cm^{-1} appeared as in the disc spectrum. The n.m.r. spectrum, due again

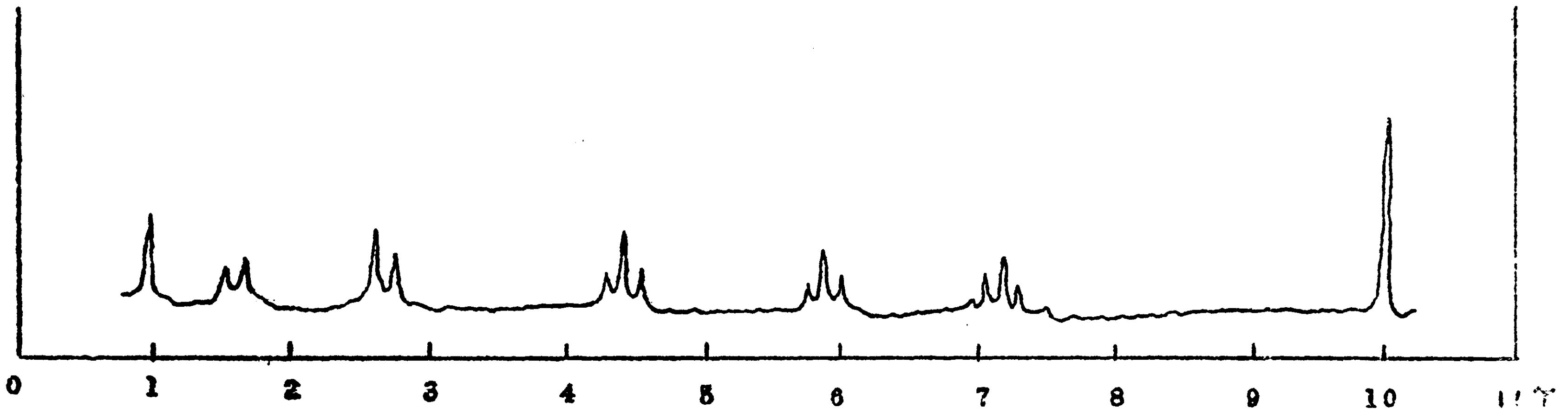


Fig. 1.

N.m.r. spectrum of By-product 1.

to insolubility, had to be recorded in trifluoracetic acid. No integration was possible at this time, but the spectrum itself was of an unusual and simple pattern and is reproduced in Fig. 1. The following signals were observed:-
at -1.33τ (proton of trifluoracetic acid), 1.63τ (doublet), 2.7τ (doublet), 4.46τ (triplet), 5.88τ (triplet), 7.2τ (quintet). None of these was immediately assignable to any particular structure, and further chemical evidence was sought.

Preparation of the p-bromophenacyl ester was attempted and yielded a yellowish solid whose i.r. spectrum indicated that it could be a mixture of starting material and reagent. T.l.c. however showed the solid to be comprised of no less than eleven components, three of which were present in considerable amounts, but could not be separated from the mixture.

Wolff-Kishner reduction of the unknown compound was uninformative. The product was acidic in character but appeared to be a mixture. The i.r. spectrum, although indistinct, did indicate strong hydroxyl absorption and weak carbonyl absorption in the region of 1700 cm^{-1}.

Treatment of the unknown compound with hydriodic acid-acetic acid to test for the presence of any residual ether link similarly gave no useful results; the paucity and impurity of the product precluded any further investigation.

The structure of this by-product thus remains unknown.

By-product 2.

A second by-product was obtained from this reaction but present in such small amounts that it appeared detectable only when the reaction was carried out on a large scale. It was first observed as a solid contaminant of homochroman-5-one and could be precipitated out of the mixture by addition of ether. The crude material was recrystallised as a finely-divided white solid from chloroform-light petroleum mixtures. The solid sublimed at 214° to laths which then melted at 238°. A bright orange 2:4-dinitrophenylhydrazone was readily obtained (m.p. > 320°).

Microanalysis of the unknown compound did not give an exact empirical formula but mass-spectrometry showed it to have a molecular weight of 324. The microanalysis was then in sufficient agreement with this figure to indicate a molecular formula of $C_{20}H_{20}O_4$.

The i.r. spectrum contained no hydroxylic or acidic absorption bands, a single sharp carbonyl band at 1680 cm^{-1}, aromatic absorption at 1600 cm^{-1} but only a few weak bands in the region 900-650 cm^{-1}. The positions and intensities of these latter bands were such as to prohibit an unequivocal recognition of benzene substitution patterns.

Further chemical evidence for the presence of one carbonyl group (or two identical or very similar carbonyl groups) came from Wolff-Kishner reduction of the unknown compound. Although a mixture of products was obtained, there was isolated, on chromatography, a white crystalline solid, m.p. $128-130^{\circ}$ with a distinctive odour and whose i.r. spectrum showed complete absence of carbonyl absorption. A number of bands were present in the region 900-650 cm^{-1} which again could not be unambiguously assigned to any particular benzene substitution pattern. Lack of material prevented any further investigation of this compound and of other fractions obtained by chromatography.

On the basis of the limited evidence obtained it is possible to postulate that this by-product could have arisen from elimination of two molecules of water between two molecules of -phenoxybutyric acid to give a diketone of formula $C_{20}H_{20}O_4$. This diketone may have two ortho-substituted benzene rings as in (115a), two para-substituted benzene rings (115b) or one ortho and one para-substituted ring (115c). The size of the centre ring in each case would be large enough to permit any of these. The weak absorptions in the i.r. spectra in the region 900-650 cm^{-1} as stated before gave no indication as to the nature of the substitution pattern.

Appendix II

Following the observation that the olefin (91) appeared to suffer deterioration on standing in air at room temperature, deliberate attempts to oxidise the olefin in air were made.

A constant stream of air was bubbled through a carbon tetrachloride solution of freshly-distilled, carbonyl-free olefin for 2 weeks. The product proved to be an inseparable mixture of compounds but the i.r. spectrum indicated two new carbonyl absorptions, at 1720 and 1680 cm^{-1}. The mixture also gave an orange-yellow precipitate on treatment with an acidic solution of 2:4-dinitrophenylhydrazine.

The experiment was repeated in basic solution, passing air through a solution of the olefin in alcoholic potassium hydroxide. Considerable darkening of the solution was observed. The product was shown by t.l.c. to consist of the starting olefin accompanied by very small amounts of a slower-moving compound. The i.r. spectrum of the mixture showed broad carbonyl absorption in the region of 1700 cm^{-1}; a 2:4-dinitrophenylhydrazone (yellow-orange needles) was obtained, m.p. 115-120°. Lack of material prevented further investigation of this derivative.

Repetition of the above experiment with the addition of heat yielded a minute quantity of a low melting solid which could not be purified but whose i.r. spectrum showed both carbonyl and strong hydroxyl absorptions.

Although no identifiable material was isolated during the above reactions there was evidence that decomposition of the olefin in air did take place to a pronounced extent. There are indeed analogies[86] for the autoxidation of allylic compounds and it is possible that oxidation of the olefin may take place by a radical mechanism such as shown. (Scheme C). If the initial step were the production of the allylic radical (116), this could react with oxygen, itself a biradical to give (117). The latter, by abstraction of a hydrogen atom from a second molecule of olefin would give the peroxide (118) and enable the chain reaction to continue. Decomposition of the peroxide itself is then also possible.

Appendix III.

(a). The solid removed from the acetate (110; R = $COCH_3$)

The solid deposited from the acetate (110; R = $COCH_3$) [p. 61] on standing was recrystallised from light petroleum as colourless needles, m.p. 95-96°. Microanalysis indicated an empirical formula of $C_{14}H_{16}O_5$. The i.r. spectrum (carbon tetrachloride) showed one strong carbonyl absorption (1750 cm^{-1}) and C - O absorption (1245, 1222 cm^{-1}). The ϵ value of the carbonyl band (1400) corresponded to the presence of two ester groups. The aromatic absorptions were normal and did not indicate conjugation with a double bond. From the evidence obtained up to this point, it was deduced that the unknown solid was a diacetate which did not contain a double bond conjugated to an aromatic ring. This diacetate could have been produced

(i) by acetylation of a diol produced by the action of selenium dioxide on the olefin (91), or

(ii) by action of acetic anhydride or acetic acid on the olefin itself or on the allylic acetate (110; R = $COCH_3$).

On this basis, a number of structures was possible, including the 1:2-diacetate (119) (<u>cis</u> or <u>trans</u>) and the 1:3-diacetate (120). On the evidence of the i.r. spectrum, no vinyl acetate could be present. If one were to assume that a double bond shift had taken place initially in the olefin, the diacetate (121) (cis or trans) would also be a possible structure.

It was hoped that n.m.r spectroscopy would eliminate at least some of the possible structures. The results, however, were not immediately in agreement with the evidence already obtained. Signals were recorded at 2.7τ (aromatics), 3.8τ (appearing as a slightly broadened singlet, i.e. sub-splitting may be present, but not discernible), 4.6τ (triplet with barely discernible sub-splitting), 5.8τ (triplet), 7.6τ (triplet), 7.8τ (singlet), 7.95τ (singlet). Apart from the signals given by the aromatic protons, the only other assignment made was to the methyl protons of the two acetate groups (7.8τ, 7.95τ). Assignment of the other peaks does not appear feasible on the basis of any one structure, especially since integration of the spectrum was not possible.

Hydrolysis of the diacetate was attempted but under acidic catalysis yielded seven inseparable compounds, none of which could be identified.

(b) The solid removed from the alcohol (110; R = H) [p. 62.]

The solid precipitated from the alcohol (110; R = H) by addition of ether was recrystallised from dioxan-ether mixtures as white laths, m.p. 140-143°. The solid was insoluble in most organic solvents, but soluble in hydroxylic solvents, including water. Microanalysis indicated an empirical formula of $C_{10}H_{12}O_3$. The i.r. spectrum (nujol) showed hydroxyl absorption (ν max 3300 cm^{-1}) and unconjugated aromatic absorption. No solution spectra were possible due to the extreme insolubility of the compound. The u.v. spectrum showed λ max 256-264 mμ (ϵ, 1650-1600) and 292 mμ (ϵ, 224). An attempt was made to record the n.m.r. spectrum but great difficulty was experienced in finding a suitable solvent. It was thought possible to record low τ-values in acetone solution and high τ-values in pyridine solution since the unknown compound was soluble in both these solvents. The results were however invalidated by the discovery that the compound reacted in some way with pyridine. (Comparison of the pyridine solution spectrum with that of pyridine alone showed this).

Mass-spectrometry did not give a parent ion at mass 180 as expected from the empirical formula, but showed the heaviest ion to be of mass 162. This may be rationalised on the assumption that water (mass 18) is easily lost from the compound and that no parent ion is in fact obtained. This is a common occurrence with alcohols, few of which are known to give parent ions but generally show the heaviest ion at mass (parent - 18). The strongest peak in the mass-spectrum of the unknown compound occurred at mass 144, i.e. a further loss of 18 mass units from 162. Such results indicated that the compound could be a diol, of mass 180, which would be expected to undergo a loss of two molecules of water to give the observed results.

Confirmation of the compound as a diol was then sought and in so doing a connection was established between it and the unknown diacetate (p.85). Acetylation of the supposed diol with acetyl chloride in pyridine gave a solid diacetate which was shown to be identical with that already isolated. Elucidation of the structure of the diol could thus provide also the structure of the diacetate and might give some insight into the mode of formation during the selenium dioxide reaction.

The problem was approached from two different angles - reactions of the diol itself, and attempted preparation of the same diol from other starting materials.

On treatment with an acidic solution of 2:4-dinitrophenylhydrazine, the diol failed to give any derivative. Had one alcohol group been adjacent to the ether oxygen atom (i.e. on C_2), the hemiacetal thus formed would be expected to open in acidic solution and yield the 2:4-dinitrophenylhydrazone of the corresponding aldehyde.

Treatment of the diol with hydriodic acid-acetic acid to establish the presence of the ether linkage gave inconclusive results and a mixture of products was obtained.

Oxidation of the diol was carried out initially with manganese dioxide in a mixture of carbon tetrachloride and chloroform. The product, a viscous yellow oil showed νmax 3350, 1700(sh), 1680 cm^{-1}. This would be in agreement with a structure such as the diol (122) where the benzylic hydroxyl group could be oxidised to a carbonyl function and the second hydroxyl group would be unaffected by manganese dioxide. The product did however appear to be a mixture and both yellow and orange-red 2:4-dinitrophenylhydrazones were obtained. Chromatography of the mixture of derivatives failed to give a satisfactory separation. One derivative was isolated in a pure state (orange needles, m.p. 261-263°) but in insufficient quantity to be of further use.

Jones's oxidation of the diol likewise gave a mixture of products which in this case may have been due to incomplete oxidation. The i.r. spectrum of the crude product showed two carbonyl bands of equal intensity (ν max ca. 1720, 1670 cm^{-1}), and residual hydroxyl absorption. If the unknown compound were a 1:2-diol as in (122), oxidation under the above conditions would give an α-diketone whose carbonyl groups would be expected to absorb in the regions observed, there being little interaction between the carbonyl groups of such a diketone.

Further attempts were therefore made to establish the diol as being of the vicinal type. No acetonide could be obtained from the diol nor was an adduct given with dicyclohexylamine and both these experiments were rejected as being inconclusive.

Were the diol either the 3:4-dihydroxyhomochroman (123) (cis or trans) or the isomeric 4:5-dihydroxyhomochroman (122 (cis or trans) it would be possible to establish the vicinal relationship of the hydroxyl groups and to differentiate between these two structures by cleavage of the diol.

Since lead tetra-acetate[87] is known in some instances to cause acetylation via a radical mechanism, the reagent chosen was sodium periodate. (122) on cleavage should give the dialdehyde (124) which on oxidation would give o-carboxyphenoxypropionic acid (125) while (123) should give the dialdehyde (126) oxidisable to the diacid (127). Since aldehydes were considered more difficult to work with, it was intended that comparisons should be made on the basis of the corresponding acids. Whilst cleavage of the diol was in progress, attempts were made to synthesise the acids (125) and (127). o-Carboxyphenoxypropionic acid (125) was readily obtained by oxidation of o-formylphenoxypropionic acid (prepared by the same method as o-formylphenoxyacetic acid (63)). The required acid (125) was a solid, m.p. 120 whose i.r.

spectrum showed the two expected carbonyl absorptions, ν max 1730 cm^{-1} (aliphatic acid) and 1690 cm^{-1} (aryl acid).

A successful synthesis of the other required diacid (127) was not achieved. Although, unlike the first acid (125), this diacid was known in the literature, it was felt that preparation of a sample was necessary so that a true comparison between it and the ultimate product of cleavage of the diol could be made. The synthesis was attempted by three different methods. In the first two, the essential stage was the preparation of o-hydroxy-α-toluic acid (128), a known acid which had already been prepared by several methods, although all in low yield. Erlenmeyer[88] reported a synthesis of (128) via an azlactone intermediate (129) formed from salicylaldehyde. (129) on treatment with hydrogen peroxide and sodium hydroxide was said to give the required acid. At each stage the production of by-products was also reported. Erlenmeyer's method was followed but yielded a mixture of products which could not be satisfactorily separated. Chromatography did yield one solid thought to be the required acid (128) but the yield and impurity of this compound rendered it of little value for continuing the synthesis.

Attention was then turned to synthesis of the required acid (128) from reaction of o-chlorophenol acetate and diethyl malonate reported as giving (128) in 34% yield[89]. o-Chlorophenol was readily acetylated in 98% yield and added to diethyl malonate containing solid sodium hydroxide and copper powder as catalyst. The product was shown (t.l.c.) to be a mixture of three compounds, none of which was diethyl malonate. The crude mixture was hydrolysed and decarboxylated. The only product which could be isolated from the reaction was found to be o-chlorophenol and this method was therefore rejected.

One more attempt was made to obtain the diacid (127). It was hoped to treat o-allylphenol with chloracetic acid to give (130) which on oxidation should yield the desired diacid (127). Allyl phenyl ether[90] was prepared by the standard method, by condensation of phenol with allyl bromide and the product converted to o-allylphenol in 96% yield. The latter was treated with chloracetic acid as in previous reactions (p. 30) and from the reaction mixture a white solid was isolated, m.p. 145-147° (from water). Microanalysis of this solid gave results corresponding to those expected for a molecular formula of $C_{11}H_{12}O_3$. The i.r. spectrum, however, was not in agreement with the expected structure. Apart from broad hydroxyl absorption of the acidic type, this showed strong absorptions at ν_{max} 1740, 1705, 1380, 1240, 915, 760, 700 cm^{-1}. The positions of these bands were not what would be expected for the required acid (130) or its possible double-bond isomer (131). Although absorption was present at 915 cm^{-1}, it was not accompanied by any other band in the region 995-985 cm^{-1}, usually found in double-bonded compounds of the vinyl type. On the other hand, were the compound the isomer (131), one would expect evidence of conjugation of the double bond with the aromatic ring and an absorption band attributable either to a trans double bond (ca. 960 cm^{-1}) or a cis double bond (ca. 690 cm^{-1}). The band at 1380 cm^{-1} does however suggest the presence of a methyl group.

The carbonyl band at 1740 cm^{-1} was much more intense than that at 1705 cm^{-1} which would be the position expected for an aliphatic carboxylic acid. One possible explanation for this is that partial lactonisation of the acid onto the double bond of the side chain may have taken place, giving rise to the 1740 cm^{-1} band. Oxidation of the compound with alkaline permanganate was essayed but gave only unchanged starting material.

No further attempts to prepare the diacid (127) were made at this stage in view of the results obtained from periodate treatment of the unknown diol.

Cleavage of the diol with sodium periodate was hampered from the start by the small quantity of material available and by its insolubility. An ethanolic solution of the diol on treatment with sodium periodate in water gave a viscous semi-solid oil. The i.r. spectrum of this material showed two separate carbonyl absorptions (ν max ca. 1725 and 1690 cm^{-1}) accompanied by a band of medium intensity at 3500 cm^{-1} and a weak band near 2750 cm^{-1}. The oil yielded no bisulphite compound but gave a precipitate with an acidic solution of 2:4-dinitrophenylhydrazine. The precipitate however decomposed on warming. Since the amount of material available was small it was decided to oxidise it in the crude state rather than suffer losses by purification. Oxidation with potassium permanganate in acetone yielded a minute amount of an intractable oil from which no information was obtained, while oxidation with alkaline permanganate gave a brown sticky oil whose i.r. spectrum, apart from showing acidic hydroxyl absorption, was indistinct and could not be used for comparative purposes.

The limited information obtained from these experiments gave some indication that the diol was most probably one of the two possible isomers (cis or trans) of 4:5-dihydroxyhomochroman (122), since cleavage with periodate gave a product containing both aryl and aliphatic aldehydes.

A means of preparing either or both of these isomers was therefore sought. Treatment of homochroman-5-one with selenium dioxide could theoretically give the α-diketone (132) which on reduction would give the required diol or diols (122). The reaction was carried out in the usual way but yielded predominantly unchanged starting material. A small amount of another compound was obtained which gave a slow positive reaction with methanolic ferric chloride but failed to give any test characteristic of α-diketones. Reduction of this material with sodium borohydride did not give any tractable material.

Hydrolysis of the α-bromoketone (85) with silver oxide gave a hydroxy-ketone which it was hoped to reduce to 4:5-dihydroxyhomochroman, but sodium borohydride treatment of the hydroxy-ketone proved unsuccessful, an inseparable mixture of compounds resulting.

The olefin (91) was epoxidised, and it was anticipated that opening of the epoxide under acid catalysis would give <u>trans</u>- 4:5-dihydroxyhomochroman. This would either be identical with the unknown diol or would be different from it, leaving the possibility that the unknown solid was <u>cis</u>-4:5-dihydroxyhomochroman.

Epoxidation was carried out with perbenzoic acid[91] in dry chloroform. Stirring the reaction mixture with solid calcium hydroxide failed to neutralise it and neutralisation was accordingly completed with aqueous sodium hydrogen carbonate. As a result, the epoxide itself was not isolated and the product was in fact a monobenzoate alcohol, the most probable isomer being the one shown (133). This could not be hydrolysed in anhydrous conditions with sodium methoxide, and was therefore refluxed in methanolic potassium hydroxide. The product, a viscous sticky oil appeared to be a mixture of compounds which could be separated into two components by solubility differences. The portion of the product soluble in light petroleum was an oily, low-melting solid which could not be induced to crystallise. Its i.r. spectrum indicated that it was an alcohol and it was therefore acetylated. The product, a white crystalline solid, (m.p. 100-103°) was found to have the molecular formula $C_{14}H_{16}O_5$, i.e. isomeric with the "diacetate" isolated from the selenium dioxide reaction on the olefin (91) (see p. 85). The i.r. spectra of these two compounds were dissimilar and on admixture of the two samples a depression of m.p. was observed.

That part of the product from hydrolysis of the monobenzoate alcohol which was insoluble in light petroleum was a white crystalline solid identical (i.r.; m.p.) with the unknown diol (p. 86). Acetylation of this solid gave the same diacetate as previously obtained (p. 85).

Since two different, isomeric diacetates were obtained, one may conclude, by extrapolation, that two isomeric diols were first obtained from epoxidation of the olefin. The explanation for this is not at all clear and one cannot assign any unambiguous structure to either of the diols or the diacetates. If opening of the expected epoxide (134) proceeded in the normal way, the only diol which should be produced would be the trans isomer (122a). The other diol obtained may be the corresponding cis diol, arrived at by a completely different route. A more satisfactory explanation would be that the second diol was also a trans diol, but derived from the isomeric olefin (135) via the appropriate epoxide. This is based on the assumption that the conjugated olefin (91) may first undergo double bond shift under acid conditions.

The unknown diol obtained previously (p. 86) could therefore have any one of a number of possible structures. Failure to form an acetonide and the nature of the product from periodate cleavage of the diol lend weight to the argument that the most probable structure for this particular diol is (122a).

EXPERIMENTAL:

General

Melting points were recorded on a Kofler microscope hot stage and are uncorrected. Routine infra-red spectra of liquid films and nujol mulls were recorded on Perkin Elmer 137 and Unicam S.P. 200 spectrophotometers. (Accuracy ± 10 cm^{-1}). Quantitative infra-red absorption spectra were determined on a Perkin Elmer model 13, and Unicam S.P. 100 double-beam spectrophotometer equipped with an S.P. 130 sodium chloride prism-grating double monochromator operated under vacuum conditions (Accuracy ± 1 cm^{-1}). Ultra-violet absorption spectra, measured on a Perkin Elmer model 137 U.V. spectrophotometer and Unicam S.P. 500 and S.P. 800 spectrophotometers, refer to solutions in ethanol unless otherwise stated.

Nuclear magnetic resonance spectra were determined on A.E.I. RS2 (60 megacycles) and Perkin Elmer RS10 (60 megacycles) spectrometers, and mass-spectra on A.E.I. MS2 and MS9 spectrometers.

Gas-liquid chromatographic data were recorded with a Pye "Argon" Chromatograph equipped with a ^{90}Sr detector. Thin-layer chromatography (t.l.c.) was carried out with Kieselgel G silica in 15% ethyl acetate-light petroleum unless otherwise stated.

Light petroleum refers to that fraction b.p. 60-80° unless otherwise stated.

EXPERIMENTAL - PART I.

o-Formylphenoxyacetic acid (63)

(i) Method I: Reflux time 20 hours

The method followed was according to Katz[59]. Chloracetic acid (52g.; 0.55 mole), salicylaldehyde (61.6g.; 0.5 mole) and sodium hydroxide (60 g.; 1.5 mole) in 500 ml. water were heated under reflux for 20 hours. The mixture was not homogeneous and was alkaline to litmus. Chloracetic acid (35 g.) and sodium hydroxide (40 g.) were added and the mixture heated under reflux for a further 15 hours. The cooled solution was acidified with hydrochloric acid (6N), yielding a brown oil (which hardened on standing) and a fine yellow precipitate. Both were dissolved in aqueous sodium carbonate, the solution filtered, washed with ether and acidified. The precipitate was a mixture of oil and solid. The latter was soluble in hot water from which it crystallised as fine yellow needles, m.p. 165° and 178°. Attempted recrystallisations from aqueous ethanol or acetic acid gave only amorphous material. On admixture with the product from (ii) (below) a depression of m.p. was observed. The material was identified by comparison of i.r. spectra as o-carboxyphenoxyacetic acid (66).

(ii) Method I. Reflux time 2 hours.

A mixture of freshly distilled salicylaldehyde

(40.55g.; 0.25 mole), chloracetic acid (34.5g.; 0.3 mole), and sodium hydroxide (40g.; 1 mole) in water (350 ml.) was heated under reflux for 2 hours. The cooled mixture on acidification (sulphuric acid, 6N) gave an oil which was extracted into ether. The ethereal solution was washed several times with aqueous sodium hydrogen carbonate which was then acidified, giving a finely divided yellow precipitate which was collected by filtration (6.9g.; 11.5%). The solid was recrystallised from water as fine yellow needles, m.p. 129-131°. The i.r. spectrum (nujol) showed ν_{OH} at 3300 cm^{-1} and ν_{CO} at 1750 cm^{-1} (ϵ-lactone), 1715 cm^{-1} (aliphatic acid) and 1675 cm^{-1} (aryl aldehyde).

(iii) Method II.

The acid (63) was prepared according to the method of Zubrys and Siebermann[60]. From 36.6 g. (0.3 mole) of salicylaldehyde, the yield of the required acid (63) was 30.7 g. (57%), recrystallised from water as cream-coloured needles, m.p. 130-133°. The i.r. spectrum of the product was identical with that of the product obtained in (ii) (above).

The Perkin reaction on o-formylphenoxyacetic acid (63)[61]

(i) The acid (63) (2g.), acetic anhydride (10g.) and anhydrous potassium acetate (6g.) were warmed together for 100 minutes; the resultant viscous oil was poured into water and solid sodium hydroxide added until the solution was alkaline to litmus. Filtration and acidification of the filtrate (dilute sulphuric acid) yielded a brown solid (0.25g.; 11%) which was recrystallised from water as yellow needles, m.p. 197°. The i.r. spectrum showed hydroxyl absorption of the carboxylic acid type and carbonyl absorption at 1680 cm^{-1}. The u.v. spectrum had λ_{max} 269 mμ (logϵ, 4.02). On admixture with a sample of coumarilic acid (68), the m.p. of the product was undepressed. The i.r. spectra of the two materials corresponded.

(ii) The acid (63) (20g.), acetic anhydride (100g.) and anhydrous potassium acetate (60g.) were heated under reflux for 90 minutes and the reaction mixture worked up as above. The product, a yellow solid (9.72g.; 40%) was recrystallised from water as pale yellow needles, m.p. 225-227°. (Found: C, 59.39; H, 4.79. $C_{11}H_{10}O_5$ requires C, 59.44; H, 4.54 %). The i.r. spectrum showed hydroxyl absorption of the carboxylic acid type, and carbonyl bands at 1725 cm^{-1} (aliphatic acid) and 1690 cm^{-1} ($\alpha\beta$-unsaturated acid) in addition to a weak band at 940 cm^{-1} (trans double bond). The u.v. spectrum showed λ max 276 mμ (log ϵ, 4.22) and 324 mμ (logϵ, 3.91).

Condensation of o-formylphenoxyacetic acid (63) with malonic acid (92).

(i) A solution of malonic acid (14.5g.) and o-formylphenoxyacetic acid (63) (11.3g.) in pyridine (30 ml.) containing o.5 ml. piperdine was warmed (steam-bath) for 1 hour, then boiled for 5 minutes. The cooled reaction mixture was poured into water, and acidified with dilute hydrochloride acid, giving a yellow precipitate. The latter was filtered off, washed with dilute hydrochloric acid, with water and dried. The product (3.3g.; 23%) was recrystallised from water as yellow needles, m.p. 193-195°. On admixture with coumarilic acid the m.p. was undepressed.

(ii) A solution of malonic acid (69.3g.; 0.6 mole) and o-formylphenoxyacetic acid (63) (60g.; 0.3 mole) in pyridine (133 ml.) containing 10 ml. piperdine was heated as described above. The cooled solution was poured into 1.3 l. cold water and acidified slowly with 170 ml. concentrated hydrochloric acid. The yellow precipitate was filtered off, washed with cold water (4 x 150 ml.) and redissolved in a solution of sodium hydroxide (54 g. in 1 l. water). The solution was filtered, diluted with water (400 ml.) and acidified with 1:1 hydrochloric acid (400 ml.). The precipitate was filtered, and washed with water (3 x 50 ml.). The product (50g.; 71%) was recrystallised from water as yellow needles, which melted at 207° to recrystallise as rhombs, m.p. 225-226°. It could also be recrystallised directly from aqueous methanol as yellow rhombs, m.p. 225-227°. The material was identified as o-coumaroxyacetic acid (64), identical (i.r., m.p.) with that obtained from the Perkin reaction (ii).

Coumarilic acid (68).

The acid was prepared by the standard method[62]. From 0.1 mole coumarin, the yield of the intermediate dibromocoumarin was 62%. 18.5g. (0.6 mole) of the dibromide gave 9.1g. (82%) coumarilic acid (68). The crude acid was purified by solution in aqueous sodium hydrogen carbonate, filtration and acidification of the solution. The precipitate was recrystallised from aqueous ethanol (1:1 by volume) as white needles, m.p. 189-190.5°.

Dihydrocoumarilic acid (69).

Coumarilic acid (68) (100 mg.), in ethanol, was reduced in an atmosphere of hydrogen, using 5% palladium-charcoal as catalyst. The uptake of hydrogen was 14.8 ml. (1 molar equivalent = 13.8 ml. hydrogen at N.T.P.). After filtration, the product (94 mg.; 93%) was recrystallised from aqueous ethanol as white needles, m.p. 116.5°.

Reductions.

(a) Product from Perkin (i) reaction, m.p. 197°.

The acid (92 mg.) in ethanol was reduced in an atmosphere of hydrogen with 5% palladium-charcoal as catalyst. The uptake of hydrogen was 13.9 ml. (1 molar equivalent = 12.7 ml. hydrogen at N.T.P.). The reaction mixture was filtered and evaporated to yield a yellowish solid (74 mg.; 80%) which was recrystallised from aqueous ethanol as white needles, m.p. 114-116°. On admixture with dihydrocoumarilic acid the m.p. was undepressed.

(b) Product from Perkin (ii) reaction, m.p. 225-227°.

A solution of the acid (2.22 g.) in 10% sodium hydroxide solution (15 ml.) was reduced in an atmosphere of hydrogen over 5% palladium-charcoal (300 mg.) as catalyst. The uptake of hydrogen was 264 ml. (1 molar equivalent = 224 ml. hydrogen, at N.T.P.). The reaction mixture was filtered. Acidification of the filtrate (to Congo Red) with dilute hydrochloric acid gave a yellow precipitate (1.41 g.; 63%). Recrystallisation from water gave the product as pale yellow needles, m.p. 141°. (Found: C, 58.64; H, 5.39. $C_{11}H_{12}O_5$ requires C, 58.93; H, 5.35%).

On admixture with the product from (a) above, the m.p. was depressed. The i.r. spectrum showed a single carbonyl band at 1715 cm^{-1}, aromatic absorption (1600 cm^{-1}) being of considerably reduced intensity. The u.v. spectrum showed λ max 275 mμ (logϵ, 3.22).

Permanganate Oxidations.

(a) o-Formylphenoxyacetic acid (63).

Potassium permanganate (4.5 g.; 0.03 mole) was heated in water (90 ml.) until solution was complete. A solution of the acid (63) (3.6 g.; 0.02 mole) in water (75 ml.) containing potassium hydroxide (1.12 g.) was then added. The internal temperature was allowed to rise to 75-80° and maintained for 1 hour. The hot reaction mixture was filtered, the residue boiled with water (100 ml.) and filtered. The combined filtrates were acidified with 10 ml. concentrated sulphuric acid in 30 ml. water, to give o-carboxyphenoxyacetic acid (66) (3.2 g.; 80.6%) as a white crystalline solid. This was recrystallised from water as white plates, m.p. 190-191.5°; ν_{CO} nujol 1720 cm^{-1} (aliphatic carboxylic acid) and 1680 cm^{-1} (aryl carboxylic acid).

(b) Product from Perkin (i) reaction, m.p. 197°.

The acid (2.16g.) was dissolved in aqueous potassium hydroxide (4 g. in 50 ml. water) and treated with a solution of potassium permanganate (7.03 g.) in water (10 ml.). The reaction mixture was heated for 2.5 hours then worked up as in (a) (above). The product (0.27 g.) was recrystallised from water as fine white needles, m.p. 193-194°. It was identified (i.r., mixed m.p.) as unchanged starting material.

Repetition of the oxidation with a longer period of heating gave no isolable material.

(c) Coumarilic acid (68).

Oxidation of the acid (68) was carried out as for (b). With a reaction time of 1.5 hours a minute amount of a solid, m.p. 192-194° was obtained. This was identical (i.r., mixed m.p.) with the starting material.

With a reaction time of 3 hours, no isolable material was obtained.

(d) o-Coumaroxyacetic acid (64) (from Perkin (ii) reaction).

The acid (2.22 g.) in water (40 ml.) containing potassium hydroxide (3.2 g.) was oxidised as in (a) with a solution of potassium permanganate (7.03 g. in 10 ml. water). The product (0.97 g.; 51%) was recrystallised from water as yellow needles, m.p. 185-189°. On admixture with the product from (a), the m.p. was undepressed, while on admixture with the product from (b) and from (c), the m.p. showed considerable depression.

Dihydro-o-coumaroxyacetic acid (62).

The Raney nickel used in these experiments was prepared according to the method of Tucker[93] and was stored under ethanol.

A solution of the acid (64) (36g.; 0.162 mole) in aqueous sodium hydroxide (250 ml.; 4N) was hydrogenated over Raney nickel (10g.) at a pressure of 6 Atm. The total uptake of hydrogen was 4 Atm. (≡ 6 l.). The reaction mixture was filtered and the filtrate acidified with hydrochloric acid (6N). At pH 7-8 a yellow precipitate was obtained and was removed by filtration. The filtrate was further acidified to pH 4 and a white crystalline solid was precipitated.

pH 7-8 precipitate.

The product was recrystallised from water as yellow needles m.p. 145-146°, which did not decolourise alkaline permanganate. It was identical with the dihydro-o-coumaroxyacetic acid previously obtained [Reduction (b) p. 104]. The i.r. spectra of the two materials were identical and no depression of m.p. was observed.

pH 4 precipitate.

The precipitate was recrystallised from water as white needles, m.p. 133° and 140-143°. On admixture with dihydro-o-coumaroxyacetic acid the m.p. was 133° and 143° but the i.r. spectra of the two materials differed. The i.r. spectrum of the material precipitated at pH4 showed additional bands at 800 and 786 cm^{-1}, and the material decolourised alkaline permanganate instantaneously.

The two precipitates were re-combined, dissolved in aqueous sodium hydroxide and shaken in an atmosphere of hydrogen over fresh catalyst (10g.). A further 0.7 Atm. hydrogen was taken up. The product was obtained by precipitation at pH7-8 as a white solid (21g.; 58%). It was recrystallised from water as white needles, m.p. 144-146°.

Optimum conditions were found to apply when 30g. o-coumaroxyacetic acid (64) in aqueous sodium hydroxide (250 ml.; 4N) was reduced over 30g. Raney nickel as catalyst. The reduction was complete in 22 hours. The yield of reduced acid (62) was 85%, obtained as one precipitate at pH7-8.

Pyrolysis of the barium salt of dihydro-o-coumaroxyacetic acid(62)

Attempt (i):- Acid: barium carbonate, molar ratio 1: 2.5.

The finely powdered acid (8.2g.; 0.038 mole) was stirred in 70 ml. hot water. Barium carbonate (20g.; 0.1 mole) was added slowly, with effervescence of carbon dioxide. The solution was evaporated to dryness, the residue powdered and thoroughly dried. The dry salt was placed in a Pyrex flask with a side arm connected to a receiver which was continuously water-cooled. The salt was dry-distilled under reduced pressure (16 mm.) by heating in a graphite bath above 360°. The distillate (15 ml.) was a brown liquid with a pronounced phenolic odour. It was dissolved in ether (15 ml.) and extracted with aqueous sodium carbonate (3x 5 ml.) (A), with aqueous sodium hydroxide (3x 5 ml.) (B), with brine (2x 5 ml.), and the residual ether solution dried (C).

A. Sodium carbonate extract.

Acidification and extraction with ether gave a white solid, recrystallised from water as needles, m.p. 139-143°, identified (i.r., m.p.) as the starting acid (62).

(B) Sodium hydroxide extract.

Acidification and extraction gave an oil which distilled to a brown liquid at 120-125°/20 mm. (bath). The product, which could not be induced to crystallise, possessed a pronounced phenolic odour, gave an intense purple colouration with methanolic ferric chloride and coupled with benzene diazonium chloride to give a red-brown azo dye. On treatment with bromine water a white precipitate was readily obtained. The precipitate was filtered, washed with water and recrystallised from aqueous ethanol as fine white needles, m.p. 92-93°. On admixture with a sample of tribromophenol the m.p. was not depressed. The i.r. spectrum of the liquid was superposable on that of phenol itself, showing typical broad hydroxyl absorption.

C. Neutral ethereal extract.

Removal of the solvent left an oil whose i.r. spectrum showed weak hydroxyl absorption (ca. 3500 cm^{-1}) and strong carbonyl absorptions at 1770-1760, 1750 and 1700 cm^{-1}. Two fractions were collected from distillation of the oil:-

1. A yellow liquid, b.p. $80^{o}/0.07$ mm., n_D^{19} 1.5590, whose i.r. spectrum showed ν_{OH} at 3400 cm^{-1}(s) and ν_{CO} at 1770-1760, 1750 and 1700(sh) cm^{-1}.
2. A yellow liquid, b.p. $80^{o}/0.07$ mm. (with slight decomposition), n_D^{19} 1.5606. The i.r. spectrum was entirely superposable on that of fraction 1, but showed reduced intensity of hydroxyl absorption at the expense of increased intensity of the carbonyl absorption at 1770-1760 cm^{-1}. Neither fraction gave any colouration with methanolic ferric chloride.

Hydrolysis of the material was attempted by heating it under reflux with 10% sodium hydroxide solution for 3 hours. The cooled solution was acidified and extracted with ether. The ethereal solution was washed, dried and concentrated to give a brown oil which solidified on standing. This solid, m.p. 83-85°, had a strong phenolic odour but gave no colouration with methanolic ferric chloride. The i.r. spectrum showed sharp hydroxyl absorption at 3350 cm^{-1} and strong carbonyl absorption at 1700

cm^{-1}. Attempted recrystallisation of the solid resulted only in oils. The solid was therefore distilled but yielded a liquid distillate which could not be solidified. The i.r. spectrum of this distillate corresponded to that of the material before hydrolysis, i.e. showing reduced hydroxyl absorption with a new carbonyl band at 1770-1760 cm^{-1}. The solid, m.p. 83-85°, was, however, shown to be melilotic acid (71) by comparison of the i.r. spectra. On admixture of the solid with a sample of the acid (71) (m.p. 88-89°) the m.p. was 84-87°. Attempted recrystallisation and distillation of the solid therefore must have given a mixture of the hydroxy-acid (71) and its corresponding lactone, dihydrocoumarin (70). Comparison of the i.r. spectra showed the original distillate, before hydrolysis,to consist of the same mixture of hydroxy-acid (71) and lactone (70).

Dihydrocoumarin (70)

Coumarin (1.47g.), in ethanol (30 ml.) was reduced in an atmosphere of hydrogen under pressure, using Raney nickel (2g.) as catalyst. The required lactone (70) was obtained as a yellow viscous oil which solidified on cooling (carbon dioxide/acetone) but could not be crystallised.

Melilotic acid (71)

Crude dihydrocoumarin (70) (0.6g.) was hydrolysed with 10%

sodium hydroxide solution (50 ml.) by heating under reflux for 3.5 hours. The reaction mixture was acidified, extracted with ether and the ethereal solution washed (brine) and dried. Concentration of the extract gave a solid which was recrystallised from water as off-white needles, m.p. 88-89° (lit. 82°)[94].

Attempt (ii):- acid: barium carbonate, molar ratio 1:5.

The experiment was repeated as in (i) using 8.2g. dihydro-*o*-coumaroxyacetic (62) acid and 40g. barium carbonate. The reaction was worked up as before but no material was obtained from the sodium hydrogen carbonate extract while the sodium hydroxide extract yielded phenol and the neutral ether extract gave a mixture of dihydrocoumarin (70) and melilotic acid (71) as before.

Attempt (ii):- with "cold-trap" isolation of volatile products.

The pyrolysis was carried out as in (ii) above and the receiver connected to the pump via a trap cooled in liquid nitrogen.

Distillate:- this was worked up as before and yielded phenol and dihydrocoumarin, accompanied by the corresponding hydroxy-acid (71).

Trap contents:- the material was extracted into ether and washed with aqueous sodium hydrogen carbonate (A) with aqueous sodium hydroxide (B), with brine and dried (C). The extracts were each worked up as before. Extract A gave a negligible amount of material with an indeterminate i.r. spectrum. Extract B gave phenol as before, and dihydrocoumarin (and the acid (71)) were obtained from extract C. No other material could be isolated.

Esterification of dihydro-o-coumaroxyacetic acid (62).

(a) Diazomethane

An ethereal solution of the acid (62) (3g.; 0.0134 mole) was treated with an ethereal solution of diazomethane (containing 0.04 mole). The reaction was worked up in the usual way and the product separated into acidic and neutral components. The acidic material consisted of 0.5g. unchanged starting material. The neutral fraction was a yellow viscous oil (2.18g.; 78%) which distilled to a colourless oil, b.p. 130-135°/0.07 mm., n_D^{24} 1.5062 (Found: C, 61.42; H, 6.59. $C_{13}H_{16}O_5$ requires C, 61.89; H, 6.39%). The i.r. spectrum showed ν_{CO} at 1750 and 1736 cm^{-1} and ν_{C-O} at 1250 cm^{-1}.

(b) Fischer-Speier esterification[95]

The acid (62) (23.33g.) was heated under reflux for 8 hours in methanol (150 ml.) saturated with gaseous hydrogen chloride. Excess of methanol was distilled off, leaving a red oil which was dissolved in ether. The ethereal solution was washed with aqueous sodium hydrogen carbonate (3 x 50 ml.), with brine and dried. Concentration of the ethereal solution gave the ester (73) (13.5g.; 51%) which distilled to a colourless oil, b.p. 177-178°/0.35 mm., n_D^{24} 1.5066.

(c) Methanol-sulphuric acid.

A solution of the acid (62) (61 g.) in dry methanol (350 ml.) and concentrated sulphuric acid (3 ml.) was allowed to stand at 20° overnight, then heated under reflux for 2 hours. Excess of methanol was distilled off, the residue diluted with water (200 ml.) and extracted with ether. The ethereal solution was washed with aqueous sodium hydrogen carbonate, with brine and dried. Acidification and extraction of the basic solution gave 4.44 g. of the acid (62), while the neutral ethereal solution gave 57.82g. (91%) of the required ester (73).

Attempted preparation of 2-carbomethoxyhomochroman-3-one (72a) by Dieckmann cyclisation.

(Formulae flow-sheet for this section is on p. (ix)).

(a) Sodium hydride[96]/xylene. High dilution technique[97].

In a three-necked flask fitted with nitrogen inlet, stirrer, pressure-equalised dropping funnel and condenser, were placed glass beads (3g.; 6 mm.), sodium hydride (1.3g.) and sodium-dried xylene (750 ml.). To the stirred mixture, under nitrogen, was added 0.5 ml. absolute methanol, and heating commenced. To the gently refluxing mixture a solution of the diester (73) (5.06g.) in xylene (250 ml.) was added at a rate of 0.2 ml./minute. Addition was completed over 120 hours. The mixture became deep orange in colour and solid was deposited. After addition, the reaction mixture was heated under reflux for 1.5 hours, allowed to cool and neutralised, with stirring and cooling, by drop-wise addition of glacial acetic acid (3g.) over 30 minutes. Stirring was then continued for 1 hour. As neutralisation took place the colour of the solution slowly paled and the precipitate dissolved. Water (13 ml.) was then added similarly. Precipitation of sodium acetate was induced by addition of a few crystals of the same. After filtration, the aqueous and organic layers were separated. The aqueous layer was extracted with xylene (2 x 25 ml.) and the extracts combined with the organic layer. The combined xylene extracts were washed with aqueous sodium hydrogen carbonate, with brine, dried and fractionated to remove xylene. The product (2.1g.; 47.7%) was a brown viscous oil which gave an intense purple colour with methanolic ferric chloride. The i.r. spectrum showed characteristic β-keto-ester bands, $\nu^{CCl_4}_{CO}$ at 1743 cm^{-1} (normal ester), 1723 cm^{-1} (ring ketone) and 1650 cm^{-1} (chelated ester) and λ max 1575 cm^{-1}. The u.v. spectrum, in neutral solution, showed λ max 255-260 mμ (ϵ, 3,300) and in basic solution λ max 291 mμ (ϵ, 7,800). The oil was not purified but was hydrolysed directly. It was, however, identical with the β-keto-ester later obtained in a purer state. (p.120).

Base hydrolysis; acid decarboxylation:- the oil was stirred at room temperature in 5% aqueous sodium hydroxide (48 ml.) and gradually dissolved. Stirring was continued for 1 hour. The solution was acidified to pH8, causing precipitation of an oil. Sufficient ethanol was added to effect solution and the mixture heated under reflux for 12 hours. Evolution of carbon dioxide was observed. The cooled solution was extracted with ether; the ethereal solution was washed with brine, with sodium hydrogen carbonate solution (a), with brine again and dried (B).

Extract A:- acidification and extraction with ether gave a brown oil, tending to solidify. The oil was distilled [190° (bath)/1 mm.]. with apparent decomposition to a yellow oil which partially solidified. This was identified (i.r.) as a mixture of dihydrocoumarin (70) and melilotic acid (71).

Extract B:- concentration of the ethereal solution gave a brown viscous oil which distilled to a yellow oil [125° (bath)/ 1 mm.] n_D^{22} 1.5461., whose i.r. spectrum showed a single intense carbonyl band at 1715 cm^{-1}. The ketone (61) was characterised as its 2:4-dinitrophenylhydrazone, which was chromatographed on 4:1 bentonite-kieselguhr and recrystallised from chloroform as pale orange needles, m.p. 160-161°. (Found: C, 56.39; H, 4.08, N, 16.17. $C_{16}H_{14}N_4O_5$ requires C, 56.14; H, 4.12, N, 16.37%). The u.v. spectrum of the derivative (in chloroform) showed λ max 261 mμ (ϵ 12,659) and 354 mμ (ϵ 25484).

Wolff-Kishner reduction[100] of homochroman-3-one (61).

A solution of the ketone (61) (0.5 g.), potassium hydroxide (0.53g.) and 100% hydrazine hydrate (1 ml.) in diethylene glycol was heated under reflux for 1.5 hours. Water was drained from the condenser and the temperature allowed to rise to 200°, collecting the distillate. The residue was refluxed a further 4 hours, cooled, diluted with water and extracted with light petroleum. The organic layer was washed, dried and concentrated to give a colourless liquid (0.4g.) with an anisole-like odour. The distillate was similarly extracted to give 0.02g. of the same product. The combined liquids (0.42g.; 95%) distilled to a colourless oil b.p. 60°/ 0.2 m.m., n_D^{23} 1.5370 (Found: C, 80.67; H, 7.92. $C_{10}H_{12}O$ requires C, 81.03; H, 8.17%), i.e. homochroman (60).

(b) Sodium hydride/ether[98].

Sodium hydride (4g.; 0.17 mole) anhydrous ether (200 ml.) and glass beads (4g.; 7 mm.) were stirred, with cooling, under an atmosphere of nitrogen. 0.5 ml. absolute methanol was added; a solution of the diester (25.23g.; 0.1 mole) in 100 ml. ether was added drop-wise, with cooling and stirring over 24 hours. After addition, the mixture was stirred at room temperature for 24 hours and refluxed for 24 hours, precipitating the yellow sodium enolate of the required β-keto-ester. Excess of sodium hydride was destroyed by cautious addition of moist ether, followed by 6 ml. water. The β-keto-ester was liberated on neutralisation with dilute hydrochloric acid. The aqueous layer was extracted with ether (2 x 5 ml.) and the combined organic layers washed with aqueous sodium hydrogen carbonate (A), with brine and dried (B).

Extract A:- acidification and extraction with ether gave a yellow viscous oil (2.33g.) whose i.r. spectrum contained both carboxylic acid and ester absorptions. (ν_{CO} 1730, 1710 cm^{-1}). Hydrolysis with 10% sodium hydroxide solution for 3.5 hours gave a dark brown solid which was purified by repeated solution in aqueous sodium hydrogen carbonate and precipitation with acid. The product was shown (i.r., m.p.) to be dihydro-o-coumaroxyacetic acid (62), indicating that the oil was the half-ester (74a or 74b).

Extract B:- removal of solvent left an oil (3.28g.; 48%), the required β-keto-ester (72).

Acid hydrolysis and decarboxylation.

The crude β-keto-ester (3.28g.) was heated under reflux for 1 hour with sulphuric acid (50 ml.; 6N) containing enough dioxan to give a homogeneous solution. The reaction mixture was cooled, diluted with water and extracted with ether. The ethereal solution was washed with aqueous sodium carbonate (A), with brine, and dried (B).

Extract A: acidification and extraction with chloroform gave a viscous brown oil (0.21g.) which possessed an indeterminate i.r. spectrum and could not be identified.

Extract B: removal of solvent left a brown oil (1.72g.), identified (i.r., 2.4-dinitrophenylhydrazone) as the ketone (61).

The ketone (61) was obtained by this method in 10.6% yield overall.

(c) Potassium t-butoxide/benzene[99].

Freshly cut potassium (8.5g.) was added in small pieces to dry t-butanol (250 ml.) under an atmosphere of nitrogen, and heated under reflux for 6 hours, with constant stirring. Excess of t-butanol was removed by distillation. Dry benzene (250 ml.) was added to the residue and distilled off slowly to azeotrope out the last traces of t-butanol. The procedure was repeated with a further 2 x 250 ml. benzene, distilling to dryness each time. The residue was dissolved in benzene (250 ml.) and the solution brought to reflux temperature. A solution of the diester (73) (10g.) in benzene (250 ml.) was added over 5 hours and the yellow potassium enolate of the β-keto-ester (72) was precipitated. To the cooled reaction mixture, glacial acetic acid was added dropwise, with cooling and stirring until the solution was just acid to litmus. Water (20 ml.) was added and the aqueous and organic layers separated. The aqueous layer was extracted with ether and the organic layers combined, washed with aqueous sodium carbonate (A), with brine, and dried (B).

Extract A:- acidification and extraction gave the half-ester (74a or 74b) (1.2g.).

Extract B:- concentration of the ether-benzene extract gave a viscous yellow oil (5.03g.; 52%), giving an intense purple colouration with methanolic ferric chloride. The i.r. spectrum corresponded to that of the β-keto-ester (72) previously obtained (p. 118). The product was much cleaner than those previously obtained and on distillation gave a pale yellow viscous oil, b.p. 116-120°/0.1 mm., n_D^{27} 1.5348 (Found: C, 65.66; H, 6.06. $C_{12}H_{12}O_4$ requires C, 65.44; H, 5.49%). The n.m.r. spectrum (carbon tetrachloride) was poorly resolved and did not provide conclusive proof of the presence of one isomer (72a) or the other (72b) either in the keto or enol forms. A mixture of either isomers or keto-enol forms was indicated. Signals were obtained at 2.96 τ(multiplet; aromatics), 4.65 τ(singlet), 5.55 τ(triplet, J = 4.83 c.p.s.), 6.16 τ(doublet, J = 1.35 c.p.s., 6.28 τ(doublet, J = very small), 6.64-7.3 τ(broad band), 8.39 τ(singlet), 8.58 τ(doublet, J = very small). G.l.c. on 10% Apiezon 'L' (175°) showed two peaks, R.T. = 36 and 384 secs. respectively; on 0.75% silicone at 130°C, three peaks were obtained, R.T. = 96, 264, and 480 secs. respectively. The last peak was extremely broad .

Homochroman-3-one (61)

(i) A solution of the β-keto-ester (72) (3.93g.) in methanol (30 ml.) containing potassium hydroxide (1.27g.) was allowed to stand at room temperature for 48 hours. Excess of methanol was removed under reduced pressure keeping the temperature below 50°. The residue was diluted with water (125 ml.) and extracted with ether (A). The aqueous layer was acidified (hydrochloric acid; 6N) and extracted with ether (2 x 30 ml.) (B). Both ether extracts were washed (brine) and dried.

Extract A:- concentration of the ethereal solution gave a red oil (2.03g.), $n_D^{20.5}$ 1.5440, identified (i.r.) as unchanged β-keto-ester (72).

Extract B:- removal of solvent left a bright yellow oil (1.7g., 46%) which solidified on standing to a yellow solid, m.p. 48°. The i.r. spectrum showed typical carboxylic acid absorptions. The acid was observed to undergo slow spontaneous decarboxylation at room temperature and decarboxylation was completed by heating the crude acid without solvent. A sample (1g.) was heated for 2 hours at 140-150° (bath). The cooled reaction mixture was dissolved in ether and separated into acidic and neutral materials. The acidic fraction was unchanged starting material and the neutral fraction, a brown oil (0.43g.; 54.6%) was shown (i.r.) to be the ketone (61).

The overall yield of ketone by this method was 25%.

(ii) When the hydrolysis was carried out on a larger scale (12g. β-keto-ester (72)), it was observed that the neutral fraction differed from that obtained in (i) above. The neutral fraction was a viscous yellow oil which in low concentrations gave a negative reaction with methanolic ferric chloride. On distillation the oil gave a fraction b.p. 68-70°/0.15 m.m., n_D^{22} 1.5428 whose i.r. spectrum corresponded to that of the ketone (61), and a fraction b.p. 70-80°/0.15 m.m., n_D^{23} 1.5485, giving a slight positive reaction with methanolic ferric chloride whose i.r. spectrum showed it to be a mixture of the ketone (61) and the β-keto-ester (72).

Reaction of homochroman-3-one (61) with N-bromosuccinimide-collidine.

A solution of the ketone (61) (1.64g.; 0.01 mole) in dry carbon tetrachloride (25 ml.) was heated under reflux for 48 hours with N-bromosuccinimide (2.1g.; 0.013 mole) containing a trace of benzoyl peroxide. The mixture was chilled, filtered and the filtrate washed (brine), dried and concentrated. The crude product was dissolved in a solution of carbon tetrachloride (15 ml.) containing 1.5 ml. redistilled collidine. A precipitate formed almost immediately and the mixture was warmed for 30 minutes, cooled, and diluted with water. The separated organic layer was washed with dilute hydrochloric acid (6N), with brine till the washings were neutral, dried and concentrated. The product, a brown oil (2.39g.) distilled to a pale yellow oil, b.p. 132-134°/0.4 mm. which darkened rapidly on standing and became tarry in consistency. The i.r.

spectrum showed three carbonyl absorption bands, at 1755, 1710 and 1650 cm^{-1} and would appear to indicate a mixture of products.

An ethanolic solution of the product gave a brick-red precipitate with an acidic solution of 2:4-dinitrophenylhydrazine. The derivative was chromatographed on 4:1 bentonite-kieselguhr. Elution with chloroform gave an amorphous orange-yellow solid which was discarded. Elution with 10% methanol-chloroform gave bright orange needles, m.p. 293-295° insoluble in most organic solvents but soluble in large volumes of pyridine. Recrystallisation from pyridine-chloroform mixtures gave only amorphous material (Found: C, 52.32; H, 3.66; N, 19.94%); λ max (chloroform) 255 mμ (logϵ, 4.23), 395 mμ (logϵ, 4.53), 435 mμ (logϵ, 4.47). When dissolved in pyridine, containing traces of ethanol, the derivative gave an intense purple solution. The colour could be dispensed by addition of one drop of water. The u.v. spectrum of the purple solution showed a continuous series of maxima from 345-570 mμ in addition to λ max at 312 mμ. A mass-spectrum of the derivative gave a peak due to the parent ion at 538 ($C_{22}H_{18}N_8O_9^+$); the second largest peak appeared at 341 (loss of $C_6H_5N_4O_4$).

Enol-acetylation of the β-keto-ester (72)

(a) Acetyl chloride

(i) Acetyl chloride (2.5 ml.) was added dropwise, with shaking and cooling, to a solution of the β-keto-ester (72) (3.5g.;

0.016 mole) in dry pyridine (15 ml.). The mixture was allowed to stand overnight at room temperature, marked discolouration occurring. Pyridine hydrochloride was filtered off, washed with dry ether (50 ml.) and the combined filtrate and washings washed with dilute hydrochloric acid (3 x 50 ml.), with aqueous sodium hydroxide (3 x 50 ml.; 4N), with brine (2 x 5 ml.) and dried. Concentration of the ethereal solution gave a brown oil (3.7g.) which distilled to give two fractions:-

1. A yellow oil, b.p. 138-139°/0.35 mm., $n_D^{18.5}$ 1.5341, giving a positive reaction with methanolic ferric chloride.
2. A yellow oil, b.p. 140-141°/0.35 mm., $n_D^{18.5}$ 1.5361, giving a negative reaction with methanolic ferric chloride. This was redistilled to a pale yellow oil, b.p. 139-140°/0.1 mm., $n_D^{19.5}$ 1.5350. (Found: C, 64.16; H, 5.95. $C_{14}H_{14}O_5$ requires C, 63.87, H, 5.74%). The i.r. spectrum (carbon tetrachloride) showed ν_{CO} at 1750 cm^{-1} (vinyl acetate) and at 1710 cm^{-1} (αβ-unsaturated ester). A small band at 1650 cm^{-1} was also present.

(ii) The experiment was repeated as in (i) above, but was carried out under an atmosphere of nitrogen. The reaction mixture was worked up by washing with brine only. This procedure lessened, but did not prevent decomposition of the enol-acetate and a mixture of β-keto-ester (72) and enol-acetate (81) was obtained.

Isopropenyl acetate[101].

The β-keto-ester (72) (2.2g.; 0.01 mole), isopropenyl acetate (1.5 ml., 0.01 mole) and p-toluenesulphonic acid (20 mg.) were refluxed together for 2 hours. The temperature was then allowed to rise and the distillate collected over 3 hours during which time a further quantity of isopropenyl acetate (1 ml.) was added to the reaction mixture. The distillate was treated with an acidic solution of 2:4-dinitrophenylhydrazine and the resultant precipitate recrystallised from the minimum volume of methanol as yellow needles, m.p. 127-128°. On admixture with the 2:4-dinitrophenylhydrazone of acetone the m.p. was undepressed. The reaction mixture was cooled and just neutralised with solid sodium hydrogen carbonate. Excess of isopropenyl acetate was removed under reduced pressure, keeping the temperature below 30°. The residue was extracted with ether and the ethereal solution washed with brine until the washings were neutral. The dried ethereal solution was concentrated, giving a red oil (2g.) which was distilled to give four (arbitrary) fractions, b.p. 118-125°/0.05 mm., all of which gave a positive reaction with methanolic ferric chloride. The i.r. spectrum of each fraction corresponded to that of the starting material (72).

Reaction of the enol-acetate (81) with N-bromosuccinimide.

A solution of the supposed enol-acetate (0.87g.) in dry carbon tetrachloride (30 ml.) was treated with a suspension of N-bromosuccinimide (0.74g.) in carbon tetrachloride (20 ml.) and the mixture heated under reflux for 1.5 hours. After thorough chilling, succinimide was filtered off, washed with ice-cold carbon tetrachloride and the combined filtrate and washings concentrated to give a red oil. The crude product was dissolved in fresh carbon tetrachloride and heated under reflux for 4 hours during which time hydrogen bromide was evolved (acidic reaction to moist litmus paper). The solution was washed (brine) until the washings were neutral, dried and concentrated to give a pale yellow oil (0.6g.; 69.5%), which gave a negative reaction with methanolic-ferric chloride. The oil was distilled, b.p. 150-160°/0.1 mm. but appeared to undergo slight decomposition, to give a brown viscous oil which gave a slight positive reaction with methanolic ferric chloride. The i.r. spectrum was indistinct and showed a broad unresolved carbonyl band ca. 1750-1650 cm^{-1} but did not in general correspond to that of either the enol-acetate (81) or the β-keto-ester (72). The u.v. spectrum (in neutral ethanol solution) showed λ max at 243 and 297 mμ; in basic ethanol solution λ max occurred at 259 mμ.

Attempted hydrolysis and decarboxylation.

A solution of the crude product (0.6g.) in methanol (20 ml.) containing potassium hydroxide (0.2g.) was allowed to stand at room temperature for 48 hours. Excess of methanol was removed, the residue flooded with water and extracted with ether. The ethereal solution was washed (brine), dried and concentrated to give a yellow glass (0.41g.) whose i.r. spectrum showed it to be unchanged starting material. The aqueous layer was acidified, extracted and worked up in the usual way to give a brown viscous oil (0.03g.). The i.r. spectrum showed hydroxyl and unresolved carbonyl absorptions. The oil was heated under reduced pressure (22 m.m.,) at 100° (bath) for 2 hours, giving an intractable tar. With Brady's reagent[102] an oily precipitate was obtained which was chromatographed on 4:1 bentonite-kieselguhr. Elution with chloroform gave an orange-red solid melting over a considerable range of temperature. The derivative could not be obtained in a pure state and was not identified.

γ-Phenoxybutyric acid (84).

The acid was prepared by a modification of the standard method[67]. Phenol (47g.) was dissolved in 35% sodium hydroxide solution (86 ml.) and the solution evaporated to dryness, under reduced pressure at 150-160° (bath). γ-butyrolactone (56 ml.) was added, the mixture allowed to stand overnight and the resultant solid mass heated at 270° in a metal bath for 4 hours. The cooled reaction mixture was boiled with 250 ml. water, the solution decanted and the residue boiled with a further 250 ml. water. The process was repeated until the whole of the product was in solution (700 ml.). The solution was acidified with dilute hydrochloric acid to give a light-brown oil which readily solidified on cooling. The solid was extracted into ether and the ethereal solution washed with aqueous sodium carbonate solution (3 x 100 ml.). The latter was re-acidified with dilute acid, the precipitate filtered, washed with water and dried (80g.; 89%). The product was recrystallised from light petroleum as thin white plates, m.p. 69-70°.

Homochroman-5-one (65)[66,68].

Phosphorus pentoxide (400g.) was stirred vigorously while orthophosphoric acid (240 ml., sp. gr. 1.75) was added. The stirred mixture was warmed (steam-bath) until solution was complete (2 hours). Dry, finely-powdered γ-phenoxybutyric acid (84) (16g.) was added with vigorous stirring and heating continued for a further 1.5 hours. The reaction mixture was cooled, poured onto crushed ice (3 Kg.), allowed to come to room temperature and extracted with ether. (4x). The combined ether extracts were washed with aqueous sodium carbonate, with brine and dried. Concentration of the ethereal layer afforded the required ketone (65) as an oil (10.86g.; 75%) which distilled to a colourless liquid, m.p. 82-84°/ 0.035 mm., $n_D^{19.5}$ 1.5641; $\nu_{CO}^{CCl_4}$ 1680 cm^{-1}. The ketone gave a 2:4-dinitrophenylhydrazone, orange needles, m.p. 240-246°; λ max 370 mμ (logϵ, 4.42). Wolff-Kishner reduction of the ketone was carried out as for the isomeric homochroman-3-one (61) (p. 117). On reduction, the ketone (65) (3g.) gave homochroman (60) (1.43g.; 52%), identical with the product from reduction of the ketone (61).

The sodium carbonate washings, on acidification and extraction gave a brown solid (0.94g.) which was examined separately (see Experimental, Appendix I, By-product 1, p.150).

In a repeat preparation of the ketone (65), using 32g. of the acid (84), the crude reaction mixture was extracted with ether and with chloroform. The ether extract yielded the ketone (65) as before; the chloroform extract yielded a brown oil from which a solid was deposited on standing. The solid could also be precipitated by addition of ether. It was removed and examined separately (see Experimental, Appendix I, By-product 2, p.152).

Attempted bromination[103] of homochroman-5-one (65).

A solution of the ketone (65) (3.89g.; 0.02 mole) in glacial acetic acid (40 ml.) was treated with a solution of bromine (3.82g.; 0.02 mole) in glacial acetic acid (10 ml.), added dropwise over 3 hours. On addition of water (50 ml.) to the reaction mixture an oil was precipitated which was extracted into chloroform. The aqueous layer was re-extracted with chloroform, the extracts combined and washed with saturated sodium carbonate (3 x 25 ml.), with 5% sodium bisulphite in brine (3 x 25 ml.), with brine (25 ml.) and dried. Removal of solvent left a brown oil (4g.; 69%) whose i.r. spectrum showed it to be a mixture of bromo-ketone (ν_{CO} 1695 cm^{-1}) and the starting ketone (65) (ν_{CO} 1680 cm^{-1}). A sample of the partially brominated ketone (1g.) in glacial acetic acid (25 ml.) was treated dropwise with a solution of bromine (3.5g.) in acetic acid (10 ml.). A permanent colouration was obtained with the addition of only a few ml. of bromine solution. The reaction was worked up as before. Removal of solvent left an oil which distilled to a pale yellow liquid, b.p. 120-124°/0.4 mm., n_D^{19} 1.6070. The i.r. spectrum still showed two carbonyl absorptions at 1695 and 1680 cm^{-1} of almost equal intensity.

Quinoxaline derivative[104] :- a solution of the partially brominated product (1.11g.), o-phenylenediamine (0.5g.) and sodium acetate (0.7g.) in ethanol (20 ml.) was heated under reflux for 2 hours. No precipitate was obtained; water was added to the reaction mixture and excess of ethanol removed under reduced pressure. The residue was diluted with water and extracted with ether. The ethereal layer was extracted with dilute hydrochloric acid. Basification of the acid extract with aqueous sodium carbonate caused precipitation of a finely-divided solid which was extracted into chloroform. Drying of the chloroform solution over magnesium sulphate was prohibited by strong adsorption of the material on the drying agent. The solution was therefore concentrated and the product dried by azeotropy with benzene. The product was found to be a mixture of two components, one of which (unchanged o-phenylenediamine) was removed by solution in benzene. The residual yellow solid (which possessed a green fluorescence in solution and turned red in alkali) was recrystallised from ether (5X) as pale yellow needles, m.p. 121-122° (Found: C, 77.11; H, 5.4; N, 11.14. $C_{16}H_{12}N_2O$ requires C, 77.4; H, 4.87; N, 11.28%. $C_{16}H_{14}N_2O$ requires C, 76.78; H, 5.64; N, 11.19%). A mass-spectrum showed a parent ion at 248 ($C_{16}H_{12}N_2O^+$) and strong peaks at 233 (loss of 15 mass units) and 218 (loss of 2 x 15 mass units). The i.r. spectrum showed very few absorption bands even in high concentrations, ν max 3400, 3200, 1600, 1480, 1210, 750 cm^{-1}. The u.v. spectrum showed λ max 244 mμ (log ϵ, 4.41) and 330 mμ (log ϵ, 3.98).

Preparation of the p-toluenesulphonylhydrazone[105] of homochroman-5-one (65).

A solution of the ketone (65) (2g.; 0.012 mole) and p-toluenesulphonylhydrazine (4.3g.; 0.012 mole) in methanol (20 ml.) was heated under reflux for 30 minutes. On cooling, a white crystalline solid was deposited (3.3g.; 81%). It was recrystallised from methanol as flat white plates, m.p. 147-148° (Found: C, 61.69; H, 5.58; N, 8.59. $C_{17}H_{18}N_2O_3S$ requires C, 61.81; H, 5.49; N, 8.48%), λ max 259 mμ (ϵ 1,700).

Degeneration[69, 105] of the p-toluenesulphonylhydrazone:- the derivative (2.44 g.) was heated under reflux for 1.5 hours in a solution of sodium in ethylene glycol (17 ml.; 1N). The cooled reaction mixture was diluted with water, extracted with ether and the aqueous and organic layers separated. The aqueous layer, on acidification and extraction, gave a yellowish-white solid (0.84g.), m.p. 84°. This was identified (i.r., m.p.) as p-toluenesulphinic acid. (0.84g. = 76% of yield expected). The ether layer was washed (brine) till the washings were neutral, and dried. Concentration of the ethereal solution gave a yellow oil (1.35g.), possessing a pronounced phenolic odour and giving a green colouration with methanolic ferric chloride. The u.v. spectrum of the crude oil showed λ max 268, 308 mμ. The product was partially soluble in aqueous sodium hydroxide. The base-soluble portion was an orange sticky oil (0.09g.; 8% of the total). The oil gave a green colouration with methanolic ferric chloride; its u.v. spectrum showed λ max 266, 308 mμ. The oil could not be induced to solidify and was not investigated further. The base-insoluble portion of the product was a yellow-green oil (0.97g.; 92% of the total) whose i.r. spectrum showed hydroxyl absorption. The u.v. spectrum showed λ max 268 mμ. The oil was distilled and gave four fractions:-

1. A yellow oil, b.p. 58-60°/0.07 mm., λ max 220, 265, 308mμ.
2. A green oil, b.p. 61-64°/0.07 mm., λ max 220, 265, 308mμ. The oil turned yellow on standing.

Both fractions 1 and 2 gave negative results with methanolic ferric chloride.

3. A violet oil, b.p. 64-88°/0.07 mm., λ max 269 mμ. The oil turned yellow on standing.
4. A pale yellow oil, b.p. 85-86°/0.07 mm., λ max 270 mμ. The oil gave a negative reaction with methanolic ferric chloride. The i.r. spectrum showed ν_{OH} 3500-3400 cm^{-1}, $\nu_{C=C}$ 1620 cm^{-1} but no cis double bond absorption ca. 690 cm^{-1}.

None of the fractions was identical with the olefin (91) but comparison of the i.r. spectra with that of the olefin obtained later (p. 135) showed that traces of it were present in the product.

Homochroman-5-ol. (92).

A solution of the ketone (65) (4.5g.; 0.028 mole) in methanol (30 ml.) was cooled in ice and treated with a solution of sodium borohydride (1.3g.; 0.034 mole) in water (15 ml.). The reaction mixture was allowed to stand overnight at room temperature, diluted to 90 ml. with water and extracted with ether (4 x 25 ml.) (A). The aqueous layer was acidified and extracted with ether (B).

Extract A yielded a white crystalline solid (4.4g.; 98%) and extract B gave 0.01g. of the same solid. The alcohol could be recrystallised from chloroform (needles) or aqueous methanol (cubes), m.p. 75°. (Found: C, 73.05; H, 7.05. $C_{10}H_{12}O_2$ requires C, 73.14; H, 7.04%). The i.r. spectrum showed evidence of intramolecular hydrogen-bonding, ν_{OH} 3200 cm^{-1} (free hydroxyl) and 2600 cm^{-1} (bonded hydroxyl, weak).

2:3-Dihydrobenz-1-oxepin (91).

The olefin (91) was obtained by dehydration of the alcohol (92). Two methods were employed.

(a) Boric acid[106].

The alcohol (92) (4.3g.; 0.026 mole) and boric acid (1.7g.; 0.027 mole) were ground together to a fine powder which was heated at 140° (bath) under reduced pressure (20 mm.) for 2 hours. Water formed in the reaction was removed by distillation. The olefin (91) distilled over at higher temperatures (106-108°/15 mm.) as a colourless mobile oil (2.8g.; 95%).

(b) Hydrochloric acid/methanol.

A solution of the alcohol (92) (10g.) in methanol (150 ml.) containing concentrated hydrochloric acid (10 ml.) was heated (steam-bath) for 1.5 hours, neutralised with aqueous sodium hydroxide (4N) and concentrated. The mixture was extracted with benzene. Concentration of the washed and dried benzene extract gave the olefin (91) (7.38g.; 83%) which distilled as a colourless liquid, b.p. 104°/10 mm.

The products obtained from reactions (a) and (b) were identical. (Found: C, 81.72; H, 6.68. $C_{10}H_{10}O$ requires C, 82.16; H, 6.9%). The olefin rapidly decolourised aqueous permanganate and gave instant colouration with tetranitromethane. On reduction over 5% palladium-charcoal as catalyst, the olefin gave homochroman (60), with uptake of 1 molar equivalent of hydrogen.

The i.r. spectrum showed $\nu_{C=C}$ at 1625, 700 and 660 cm^{-1} with increased intensity of aromatic absorptions. The u.v. spectrum showed λ max 255 mμ (log ϵ, 4.0) and 293 mμ (log ϵ, 3.21).

The n.m.r. spectrum (see Discussion, p. 55) gave bands at 3.0τ(multiplet, aromatics), 3.7τ(double triplet, proton on C_5; J = 12 cps and 1.9 cps), 4.3τ(double triplet, proton on C_4; J = 12 cps and 4.8 cps), 5.9τ(triplet, protons on C_2; J = 4.8 cps) and 7.56τ(octet, protons on C_3; J = 1.9 cps).

<u>Note</u>:- the olefin (91) was subject to aerial oxidation (see Experimental, Appendix II, p. 158).

3-Acetoxy-2:3-dihydrobenz-1-oxepin (110; R = $COCH_3$).

The acetate (110; R = $COCH_3$) was prepared by selenium dioxide oxidation[83] of the olefin (91). A number of modifications were employed.

(i) Selenium dioxide/acetic anhydride/2 hours.

Selenium dioxide (1.13g.; 0.01 mole) was added to a solution of the olefin (91) (3g.; 0.02 mole) in acetic anhydride (15 ml.) and the mixture brought slowly to reflux temperature. Rapid darkening of the mixture was observed. Heating was continued for 2 hours, the mixture cooled and the supernatant liquid decanted with water (100 ml.). The residual selenium was washed with water, and the washings combined and extracted with ether. The ethereal solution was run through a short column of alumina and precipitated silver[107]. (1:1 by weight) to remove colloidal selenium. (An alternative procedure was to boil the product, dissolved in benzene, over precipitated silver for 15 minutes). Removal of solvent gave a dark-brown oil from which the bulk of residual acetic anhydride was removed by distillation under reduced pressure. Distillation of the residue gave:-

1. A colourless liquid, b.p. 61°/0.03 mm. whose i.r. spectrum indicated the presence of an acetate (ν_{CO} 1730 cm^{-1}; ν_{C-O} ca. 1250 cm^{-1}) contaminated with

traces of acetic anhydride. Redistillation did not provide a pure sample of the acetate.

2. A colourless liquid b.p. 64°/0.04 m.m., whose i.r. spectrum showed it to be a mixture of an alcohol (ν_{OH} 3450-3250 cm^{-1}) and an acetate (ν_{CO} 1730 cm^{-1}). The total yield of distilled material was 0.99g. (25%).

The material obtained in this reaction was shown, by comparison of i.r. spectra of pure samples later obtained (see (ii) below and p 139) to be a mixture of the required acetate (110; R = $COCH_3$) and the alcohol (110; R = H).

(ii) <u>Selenium dioxide/acetic acid/1.5 hours</u>.

A mixture of selenium dioxide (0.6g.; 0.005 mole) and the olefin (91) (1.36g.; 0.009 mole) in acetic acid (10 ml.) was heated under reflux for 1.5 hours. The reaction mixture was worked up as in (i) with the exception that the ethereal solution was washed with aqueous sodium carbonate before being run through the alumina-silver column. Removal of the ether left a brown oil (1.5g.; 83%) whose i.r. spectrum showed no hydroxylic or carboxylic absorptions. Distillation afforded the acetate (110; R = $COCH_3$) as a pale yellow oil, b.p. 74-96°/0.4 mm.. (Found: C, 70.23; H, 6.09. $C_{12}H_{12}O_3$ requires C, 70.59; H, 5.88%); ν_{CO} 1730 cm^{-1}.

The n.m.r. spectrum (carbon tetrachloride), although not very well resolved showed the following bands:- multiplet at 2.9τ (aromatic protons); doublet at 3.5τ (J = 12.3 cps; proton on C_5); irregular multiplet centred on 4.0τ (proton on C_4); quartet centred on 4.42τ (J = 3.7 cps; protons on C_3); doublet at 5.75τ (J = 3.7 cps; protons on C_2), singlet at 7.9τ (methyl protons).

(iii) Selenium dioxide/acetic acid/1 hour.

A reaction mixture of selenium dioxide (5g.; 0.044 mole), olefin (91) (10.57g.; 0.075 mole) and acetic acid (90 ml.) treated as in (ii) gave an oil which, on distillation yielded the olefin (91) (1.18g.), the required acetate (110; R = $COCH_3$) (7.9g.; 63%) and a black tarry residue (2.67g.) which was not identified.

(iv) Selenium dioxide/acetic acid; pyridine/acetic anhydride.

In subsequent preparations of the acetate (110; R = $COCH_3$), the crude reaction mixture from the selenium dioxide oxidation was treated with a mixture of pyridine and acetic anhydride (2:1 by volume) and allowed to stand at room temperature for 24 hours. The mixture was poured into water, acidified (dilute hydrochloric acid) and extracted with ether. The washed and dried ether extract was concentrated and the product distilled to give the acetate (110; R = $COCH_3$) uncontaminated by any hydroxylic material.

Note:- It was observed that on prolonged standing, the acetate deposited large needle-shaped crystals. These were insoluble in cold light petroleum and were isolated by filtration of a light petroleum solution of the acetate. The material was examined separately (see Experimental, Appendix III, p. 155).

2:3-Dihydro-3-hydroxybenz-1-oxepin (110; R = H).

(i) Hydrolysis of the acetate (110; R = $COCH_3$) with sulphuric acid in methanol gave an oil whose i.r. spectrum showed residual acetate absorption as well as strong hydroxyl absorption (ν_{OH} 3400 cm^{-1}). Re-hydrolysis did not succeed in making the reaction go to completion and a mixture of acetate and alcohol was obtained.

(ii) Basic hydrolysis of the acetate (110; R = $COCH_3$) was carried out as on p. 120. A solution of the acetate (110; R = $COCH_3$) (1.5g.) in methanol (100 ml.) containing potassium hydroxide (1.7g.) was heated under reflux for 2.5 hours, and worked up as usual to give a brown oil (0.8 g.; 66%). Distillation afforded the alcohol (110; R = H) as a colourless oil, b.p. 94-95°/0.04 mm. n_D^{21} 1.6028. (Found: C, 73.12; H, 6.28. $C_{10}H_{10}O_2$ requires C, 74.05; H, 6.22%); λ max 255 mμ (log ϵ, 3.92) and 290 mμ (log ϵ, 3.18). The i.r. spectrum showed hydroxyl absorption at 3300 cm^{-1}, and double band absorption $\nu_{C=C}$ at 1630 cm^{-1}, with increased intensity of the aromatic bands at 1603, 1582 and 1492 cm^{-1}.

The n.m.r. spectrum (carbon tetrachloride) gave the following bands:- multiplet at 3.0 τ (aromatics); doublet centred on 3.75 τ (proton on C_5 split by proton on C_4, J = 13 cps); quartet centred on 4.09 τ (proton on C_4 split by proton on C_5, J = 13 cps, each band further split by coupling with the proton on C_3, J = 3 cps.); unresolved band at 5.6 τ (proton on C_3 and alcoholic proton); doublet centred on 5.92 τ (protons on C_2 split by proton on C_3, J = 4.5 cps).

The alcohol (110; R = H) on standing was observed to undergo deterioration. The i.r. spectrum showed ν_{CO} 1720, 1680 cm^{-1} and a precipitate was obtained with 2:4-dinitrophenylhydrazine but proved to be a mixture. Distillation of the deteriorated material did not provide any pure samples.

When the hydrolysis was carried out on a larger scale it was possible to isolate a small quantity of another material. Hydrolysis of the acetate (110; R = $COCH_3$) (7.9g.) gave the required alcohol (110: R = H) and a white crystalline solid (0.51g.) which could be precipitated out of the alcohol by trituration with ether. The solid was removed and examined separately (see Experimental, Appendix III, p. 155).

Oxidation of 2:3-dihydro-3-hydroxybenz-1-oxepin (110; R = H).

(a) Manganese dioxide.

(i) Carbon tetrachloride/7 hours.

The alcohol (110; R = H) (0.4g.) and manganese dioxide (4g.) in carbon tetrachloride (40 ml.) were stirred vigorously at room temperature for 7 hours. The reaction mixture was filtered (Celite 535) and the residue washed with hot carbon tetrachloride. The combined filtrates were evaporated to leave a very small amount of a colourless oil which on cooling gave fine white needles, m.p. 60-65°, ν_{CO} 1740 cm^{-1} (w), 1700 cm^{-1} (s) and 1680 cm^{-1} (sh;m). Treatment of the product with 2:4-dinitrophenylhydrazine gave a very small amount of an oil which was soluble in methanol and could not be induced to solidify.

(ii) Carbon tetrachloride/15 hours.

The alcohol (110; R = H) (0.8g.) and manganese dioxide (8g.) in carbon tetrachloride (80 ml.) were stirred at room temperature for 15 hours. The reaction mixture was worked up as in (i), giving a yellow oil, containing traces of solid. Distillation of the product afforded two fractions:-

1. A colourless oil, b.p. 60-88°/0.2 mm., ν_{max} 1730(s) 1660 (s), 1600(s), 1570(s), 1480(s), 710(s), 670(s) cm^{-1}. A mixture of 2:4-dinitrophenylhydrazones was obtained.

2. A yellow oil, b.p. 90°/0.2 mm.; ν max 1750(w), 1730(s), 1660(s), 1600(s), 1570(s), 1480(s), 710(s) and 670(s). Multiplicity in the carbonyl region indicated the presence of a mixture. One 2:4-dinitrophenylhydrazone was however isolated, an orange amorphous solid, m.p. 175°.

(iii). <u>Carbon tetrachloride/48 hours</u>.

The alcohol (110; R = H) (0.2g.) and manganese dioxide (2g.) in carbon tetrachloride (80 ml.) were stirred together for 48 hours and worked up as in (i) to yield a yellow oil (0.16g.) whose i.r. spectrum again showed multiplicity in the carbonyl region. T.l.c. showed four spots whose R_f values were close together and rendered separation by chromatography impracticable. A mixture of 2:4-dinitrophenylhydrazones, chromatographed on 4:1 bentonite-kieselguhr, yielded a bright orange solid m.p. 172-175°; λ max 250, 390 mμ; the derivative was identical with that obtained in (ii) above.

The product from the oxidation (0.15g.), in ethanol (20 ml.) was reduced in an atmosphere of hydrogen, using 5% palladium-charcoal (15 mg.) as catalyst. The uptake of hydrogen was 17.5 ml. (1 molar equivalent = 22.4 ml. hydrogen at N.T.P.). The product, a yellow oil, showed ν_{OH} 3500 cm^{-1} and ν_{CO} 1730 cm^{-1}. The oil gave a

2:4-dinitrophenylhydrazone, recrystallised from ethyl acetate as needles, m.p. 158-159°. On admixture with the 2:4-dinitrophenylhydrazone of homochroman-3-one (61), the m.p. was not depressed.

(b) <u>Chromium trioxide/sulphuric acid (Jones's reagent)[84].</u>

The alcohol (110; R = H) (1.64g.) was oxidised with the calculated amount of Jones's reagent. The product was a yellow oil (0.67g.; 40%) containing some solid. T.l.c. showed the product to be a mixture of four compounds; one of these was identified (R_f values) as the olefin (91). The other three were carbonyl-containing compounds. On trituration with ether, a minute amount of a white solid was obtained. The solid (m.p. 243-246°, subliming at 240°) showed ν_{CO} 1700 and 1680 cm^{-1} and gave a yellow precipitate with 2:4-dinitrophenylhydrazine solution. Lack of material prevented identification of the compound.

The residue, a viscous yellow oil, was chromatographed on alumina (grade III; neutral), eluting with light petroleum and ether-light petroleum mixtures with increasing percentages of ether. The majority of fractions obtained contained mixtures but that eluted with 2% ether-light petroleum gave an impure sample of the required ketone(75), ν_{CO} 1660 cm^{-1}. The u.v. spectrum, in neutral ethanol solution showed λ max 257 mμ (logϵ, 3.96), 265 mμ (sh.; logϵ, 3.94) and 292-300mμ (logϵ, 3.21). The u.v. spectrum in basic ethanol solution was identical with that in neutral solution.

A sample of the presumed ketone (75) (0.25g.), in ethanol, was reduced in an atmosphere of hydrogen over 5% palladium-charcoal (150 mg.) as catalyst. The i.r. spectrum of the product showed it to be a mixture of saturated and unsaturated ketones. The product gave a yellow 2:4-dinitrophenylhydrazone, recrystallised from ethyl acetate as needles, m.p. 155-159°. On admixture with the 2:4-dinitrophenylhydrazone of homochroman-3-one (61), the m.p. was undepressed.

Attempted pyrolysis[85] of 3-acetoxy-2:3-dihydrobenz-1-oxepin (110; $R = COCH_3$).

The acetate (110; $R = COCH_3$) was heated and the vapour allowed to pass through a column of packed glass helices heated in an electric furnace at 380°. The system was kept under an atmosphere of nitrogen, at 1 mm. pressure. The distillate was collected in a receiver cooled in liquid nitrogen. It was found (i.r.) to be unchanged acetate. Repetition of the procedure at 450° also gave unchanged starting material.

Attempted tosylation of 2:3-dihydro-3-hydroxybenz-1-oxepin (110; $R = H$).

(i) 48 hours.

The alcohol (8g.) was dissolved in dry pyridine (125 ml.) containing tosyl chloride (10g.) and the mixture allowed to stand at room temperature for 48 hours. The black solution was poured into water and extracted with ether. The ethereal solution was washed with dilute hydrochloric acid, with brine, with aqueous sodium hydrogen carbonate, with brine and dried. Concentration of the ethereal solution gave a semi-solid mass, shown by t.l.c. (benzene) to contain five compounds. The i.r. spectrum showed hydroxyl absorption.

(ii) 2 weeks.

A reaction mixture identical to that in (i) was allowed to stand at room temperature for 2 weeks. It was then poured into ice-cold aqueous sodium hydrogen carbonate, allowed to stand for 30 minutes and extracted with ether. The ether extract was worked up as in (i) to yield a yellow oil which could not be induced to solidify. The i.r. spectrum showed no hydroxyl absorption, weak carbonyl absorption at 1710 cm^{-1} and bands at 1350-1300, 1250, 1200, 1180, 1160, 1000, 1050, 800, 750 cm^{-1}. T.l.c. (5% ethyl acetate-light petroleum) showed two strong spots and a weak one. The product was not purified.

Treatment of the supposed tosylate (110; R = Ts) with collidine:

The crude product (2.8g.) from the above reaction was dissolved in collidine and the solution heated under reflux for 6 hours. The reaction mixture was taken up in ether and the ethereal solution washed with dilute hydrochloric acid, with brine, and dried. Removal of the ether left a brown oil whose i.r. spectrum was identical with that of the starting material.

The experiment was repeated using quinoline as solvent. Unchanged starting material was again obtained.

Reaction of the alcohol (110, R = H) with pyridine.

A solution of the alcohol (110; R = H) in pyridine was allowed to stand at room temperature for 24 hours, then worked up as usual. The product was entirely unchanged starting material.

Attempted preparation and pyrolysis of the carbonate (110; $R = CO_2C_2H_5$).

(i). A solution of the alcohol (110; R = H) (350 mg.) in dry pyridine (7 ml.) was cooled in ice. Ethyl chloroformate (2.5 ml.) was added, the flask stoppered and allowed to stand overnight at 0°. The reaction mixture was poured into water, extracted with light petroleum and the organic layer washed (dilute acid; brine) and dried. Removal of the solvent gave a yellow oil (451 mg.) with an ester-like odour, ν_{CO} at 1740 cm^{-1}, ν_{C-O} at 1250 cm^{-1}, with complete absence of hydroxyl absorption.

The crude material was dissolved in diethyl phthalate and heated at 220° for 3 hours. The product was dissolved in ether and extracted with aqueous sodium hydroxide.

Acidification and extraction of the basic solution afforded a brown viscous oil with a phenolic odour; the oil gave a negative reaction with methanolic ferric chloride but on treatment with a solution of benzenediazonium chloride a red azo dye was obtained. The i.r. spectrum although indistinct did not correspond to that of α-naphthol, but showed hydroxyl absorption ν_{OH} 3600-2600 cm^{-1}.

(ii). A solution of the alcohol (110; R = H) (2.3g.) in dry pyridine (20 ml.) was treated with ethyl chloroformate (10 ml.) as in (i), to give a yellow oil (1.99g.; 60%) which was distilled, b.p. 74-77°/0.1 mm . (Found: C, 75.13; H, 6.79%), ν_{CO} 1740 cm^{-1}. The u.v. spectrum in both basic and neutral solution showed λ max 256 and 266 mμ. T.l.c. showed only one spot. The oil was soluble in aqueous sodium hydroxide and readily gave a precipitate with a solution of 2:4-dinitrophenylhydrazine. On attempted recrystallisation, the derivative decomposed.

The oil (150 mg.) was hydrolysed in the usual way with methanolic potassium hydroxide and the product separated into neutral and acidic fractions. The neutral material was a red oil which turned green on standing. The oil gave a negative reaction with methanolic ferric chloride. The i.r. spectrum showed ν_{OH} 3400 cm^{-1} and ν_{CO} 1710 and 1680 cm^{-1}. T.l.c. showed the material to be a mixture of eight compounds. The acidic product, a yellow oil, turned red on standing, and consisted of a mixture of six compounds (t.l.c.).

Oxidation of the unknown oil (560 mg.) with potassium permanganate in acetone afforded only 27 mg. of an oil whose i.r. spectrum showed it to be largely unchanged starting material.

Reaction of 2:3-dihydrobenz-1-oxepin (91) with N-bromosuccinimide.

To a solution of the olefin (91) (5g.; 0.034 mole) in dry carbon tetrachloride (25 ml.) were added N-bromosuccinimide (6.8g.; 0.068 mole) and a trace of benzoyl peroxide. The mixture was heated under reflux for 48 hours, chilled and filtered. The filtrate was washed (brine), dried and concentrated. The crude product was dissolved in a solution of redistilled collidine (4.2g.) in carbon tetrachloride (25 ml.), and heated under reflux for 2 hours, during which a brown oil collected on the bottom of the flask. Work-up in the usual way afforded a yellow oil (4.5g.) which was chromatographed on alumina (85g.; grade III, neutral). The following materials were obtained:-

1. A yellow-green oil, eluted with light petroleum. The i.r. spectrum showed strong double bond absorption at 1620 cm^{-1} with enhanced aromatic absorptions; two new bands were present at 880 and 850 cm^{-1} while the bands observed at 700 and 660 cm^{-1} in the olefin (91) were absent.

2. A yellow oil, eluted with light petroleum, whose i.r. spectrum showed that it was predominantly the olefin (91).
3. The alcohol (110; R = H), eluted with 50% benzene-light petroleum.
4. An oil, eluted with benzene, showing ν_{OH} 3400 cm^{-1} and ν_{CO} 1700 cm^{-1}.
5. A viscous oil, eluted with benzene, showing strong hydroxyl absorption ν_{OH} 3400 cm^{-1} but no carbonyl absorption.
6. A viscous oil eluted with 10% chloroform-benzene, whose i.r. spectrum showed few peaks apart from a strong carbonyl band at 1700 cm^{-1}.

Fraction 1, which darkened rapidly on standing, was treated with maleic anhydride in refluxing benzene but failed to give any adduct.

Appendix I.

By-product 1. (see p.129).

The solid was recrystallised from water as off-white needles, m.p. 141-142°. Drying at 100° under reduced pressure led to decomposition. The material contained no phosphorus (Found: C, 66.59; H, 6.76%. $(C_{10}H_{12}O_3)_n$ requires C, 66.66; H, 6.66%). The mass-spectrum gave a parent peak at 180 mass units ($C_{10}H_{12}O_3^+$) and included strong peaks at 162 mass units (loss of 18 mass units), 136 mass units (loss of 44 mass units) and 93 mass units ($C_6H_5O^+$). The i.r. spectrum (KCl disc) showed ν max:-

3350(s), 3070(s), 1650(vs), 1600(w), 1580(vs), 1505(m), 1474(m), 1376(s), 1316(s), 1294(s), 1260(m), 1220(m), 1180(m), 1060(m), 1020(m), 847(s), 760-740(m) cm^{-1}.

The n.m.r. spectrum (trifluoracetic acid) (Fig. 1.) showed signals at -1.33 τ (singlet), 1.63 τ (doublet), 2.7 τ (doublet), 4.46 τ (triplet), 5.88 τ (triplet) and 7.2 τ (quintuplet).

The compound gave a 2:4-dinitrophenylhydrazone, crimson needles (from methanol) m.p. 116-118°. The derivative was soluble in aqueous sodium carbonate, sodium hydroxide and ammonium hydroxide.

Attempted preparation of a p-bromophenacyl ester.

The unknown compound (140 mg.) in water (1 ml.) was neutralised until the solution was just acid to litmus. A solution of p-bromophenacyl bromide (160 mg.) in rectified spirit (3 ml.) was added and the mixture heated under reflux for 4 hours. Extraction with ether gave a yellow solid, shown by t.l.c. to contain eleven compounds; the mixture was not separated.

Attempted Wolff-Kishner reduction.

The reduction was carried out as previously on 200 mg. of the unknown solid and yielded an acidic material, a viscous intractable oil whose i.r. spectrum showed residual hydroxyl and carbonyl absorptions.

Reaction with hydriodic acid/acetic acid.

The unknown compound was heated under reflux for 2 hours with a solution of constant-boiling hydriodic acid in glacial acetic acid. The reaction mixture was dissolved in ether and separated into neutral and acidic fractions by extraction with aqueous sodium hydroxide. The neutral material was a negligible amount of a yellow oil; the acidic material was an intractable oil whose i.r. spectrum showed ill-defined hydroxyl absorption and a broad unresolved carbonyl band (1700-1650 cm^{-1}).

By-product 2. (see p. 129).

The material was recrystallised from chloroform as a white finely-divided solid, m.p. 238° (with sublimation to laths at 214°) (Found: C, 73.00; H, 6.8%). The mass-spectrum showed a parent ion at 324 mass units ($C_{20}H_{20}O_4^+$) and showed strong peaks at 121 mass units ($C_8H_9O^+$), 120 mass units ($C_7H_4O_2^+$), and 92 mass units ($C_6H_4O^+$). The i.r. spectrum (nujol) showed carbonyl absorption at 1680 cm^{-1}, aromatic absorptions and weak bands at 865, 810, 780 and 725 cm^{-1}.

The solid gave a 2:4-dinitrophenylhydrazone, bright orange needles, m.p. $>$ 360°.

Wolff-Kishner reduction.

The unknown solid (20 mg.) was reduced in the usual way to give a yellow oil, shown by t.l.c. to be a mixture of four compounds. The oil was chromatographed on Woelm Alumina (5g.; grade III, neutral). Elution with light petroleum gave a white crystalline solid, m.p. 128-130° (subliming to fine needles, 110-115°). The i.r. spectrum showed complete absence of carbonyl absorption; in the "finger-print" region, bands appeared at 825, 775, 725 and 690 cm^{-1}.

Appendix II.

Aerial oxidation of 2:3-dihydrobenz-1-oxepin (91).

(i) Neutral solution.

A constant stream of air was bubbled through a solution of the olefin (91) in carbon tetrachloride for 14 days, replacing solvent lost by evaporation. Removal of solvent left an oil which readily gave an orange-yellow precipitate with a solution of 2:4-dinitrophenylhydrazine. The i.r. spectrum showed ν_{CO} 1720, 1680 cm^{-1}. On prolonged contact (several months) with air the olefin (91) was further oxidised. The i.r. spectrum of such a sample showed strong hydroxyl absorption, ν_{OH} 3500 cm^{-1} and carbonyl absorptions ν_{CO} 1720, 1680 cm^{-1}. The double bond absorptions at 700 and 660 cm^{-1} were virtually absent. T.l.c. showed six spots.

(ii) Basic solution.

Air was bubbled through a solution of the olefin (91) in methanolic potassium hydroxide for 24 hours. From the reaction mixture was isolated a yellow oil whose i.r. spectrum showed weak hydroxyl and carbonyl absorptions (ν_{CO} ca. 1700 cm^{-1}). The oil gave a yellow-orange 2:4-dinitrophenylhydrazone, m.p. 115-120°. T.l.c. of the oil showed the presence of two compounds, one of which was identified (R_f value) as the starting olefin (91).

When the reaction mixture was heated under reflux for 2 hours after being treated as above, the product was a semi-solid mass whose i.r. spectrum showed a further increase in intensity of hydroxyl and carbonyl absorptions.

Appendix III

By-product from selenium dioxide oxidation (see p. 139).

The solid contaminant of the acetate (110; R = $COCH_3$) was recrystallised from light petroleum as transparent needles, m.p. 95-96° (Found. C, 63.87; H, 6.01. $C_{14}H_{16}O_5$ requires C, 63.62; H, 6.10%). The i.r. spectrum (carbon tetrachloride) showed a single carbonyl absorption at 1750 cm^{-1} (ϵ, 1,400), ν_{C-O} at 1245 and 1222 cm^{-1} and no double bond absorptions other than aromatic.

The n.m.r. spectrum (deuterochloroform) gave bands at 2.7 τ (multiplet), 3.7 τ (possibly singlet), 4.6 τ (triplet, with indistinct sub-splitting), 5.8 τ (triplet), 7.6 τ (triplet), 7.8 τ (singlet), and 7.95 τ (singlet).

Attempted acid hydrolysis of the material gave a yellow oil, shown by t.l.c. to be a mixture of seven compounds. The mixture was not separated.

Solid contaminant of the alcohol (110; R = H) (see p.140).

The ether-insoluble solid was recrystallised from dioxan-ether as white needles, m.p. 140-143° (Found. C, 66.25; H, 6.47. $C_{10}H_{12}O_3$ requires C, 66.65; H, 6.71%). The mass-spectrum did not show the expected parent ion at 180 mass units, ($C_{10}H_{12}O_3^+$) but gave a peak at 162 mass units ($C_{10}H_{10}O_2^+$; loss of H_2O (18 mass units)) accompanied by an intense peak at 144 mass units ($C_{10}H_8O^+$; further loss of 18 mass units). The i.r. spectrum (nujol) showed strong hydroxyl absorption (3300 cm^{-1}), weak aromatic absorption and <u>ortho</u>-substitution (750 cm^{-1}). The u.v. spectrum showed λ max 256-264 mμ (ϵ 1650-1600) and 292 mμ (ϵ 224).

The n.m.r. spectrum was recorded in both acetone and pyridine but the spectra bore no correlation to each other and were rejected.

The solid gave a negative ferric chloride test and did not form a 2:4-dinitrophenylhydrazone.

<u>Acetylation</u>: on acetylation with acetyl chloride and pyridine, the solid gave a crystalline acetate, m.p. 95-96° (needles from light petroleum), identical (i.r., mixed m.p.) with the unknown diacetate (p.155).

<u>Oxidation</u>

(a) <u>Manganese dioxide</u>

The supposed diol (0.18g.) was shaken with manganese dioxide (1.8g.) in a mixture of carbon tetrachloride and chloroform (70 ml.) for 48 hours and worked up as previously to give a yellow sticky, viscous oil whose i.r. spectrum showed ν_{OH} 3350 cm^{-1} and ν_{CO} 1700 and 1680 cm^{-1}. The oil gave a mixture of 2:4-dinitrophenylhydrazones which were chromatographed on 4:1 bentonite-kieselguhr. Elution with benzene and benzene-chloroform mixtures gave only impure material, but elution with chloroform gave a deep orange solid, m.p. 261-263°.

(b) Jones oxidation.

A solution of the supposed diol (306 mg.) in acetone (50 ml.) was treated with Jones's reagent[84] until colouration in the supernatant layer indicated the presence of excess reagent. The reaction was worked up in the usual way to give a viscous oil (104 mg.) containing some solid. The i.r. spectrum showed hydroxyl absorption (3350 cm^{-1}), and carbonyl absorptions (1700 and 1670 cm^{-1}) but was not identical with that of the product from oxidation (a) above.

Attempted formation of an acetonide.

A solution of the unknown solid in Analar acetone was shaken with anhydrous copper sulphate at room temperature for 24 hours. Filtration and removal of solvent gave unchanged starting material.

Attempted formation of a dicyclohexylamine adduct[108].

A solution of the unknown solid in acetone was treated with a solution of dicyclohexylamine in acetone (2 molar equivalents) at 0°C. The only solid isolated was identified as the dicyclohexylamine-carbonic acid adduct, m.p. 61°.

o-Formylphenoxypropionic acid

The acid was prepared exactly as for o-formylphenoxyacetic acid (63) (p.100), and was obtained as a white crystalline solid, m.p. 116° (from water). (Found: C, 62.18; H, 5.63. $C_{10}H_{10}O_4$ requires C, 61.85; H, 5.19%). The i.r. spectrum (carbon tetrachloride) showed ν_{CO} 1718 cm^{-1} (aliphatic acid) and 1690 cm^{-1} (aryl aldehyde).

o-Carboxyphenoxypropionic acid (125).

An alkaline solution of o-formylphenoxypropionic acid was oxidised with potassium permanganate by the method used previously. No precipitate was obtained on acidification of the alkaline solution which was therefore concentrated to half of its volume. On cooling, the required acid (125) was deposited. It was recrystallised from water as white rhombs, m.p. 120°. (Found: C, 56.84; H, 5.04. $C_{10}H_{10}O_5$ requires C, 57.14; H, 4.8%). The i.r. spectrum (carbon tetrachloride) showed ν_{CO} 1730 cm^{-1} (aliphatic acid) and 1690 cm^{-1} (aryl acid).

Attempted preparation of o-hydroxy-α-toluic acid (128).

Method I: the method followed was that due to Erlenmeyer[88]. A mixture of hippuric acid (17.9g.), fused sodium acetate (8.2g.), salicylaldehyde (12.2g.) and acetic anhydride (30.6g.) was warmed (steam-bath) for 30 minutes. On cooling, a semi-solid mass was obtained. This was filtered and washed with methanol and water. Attempted purification by fractional crystallisation did not give any pure azlactone (129). The crude product was therefore heated under reflux with 10% aqueous sodium hydroxide (80 ml.) for 12 hours. The solution was cooled, diluted to 500 ml. with water and treated with 90% hydrogen peroxide (10 ml.). The acidic product was a yellowish solid (5.7g.) of an indefinite m.p., and giving a positive reaction with methanolic ferric chloride. Sublimation and fractional crystallisation failed to give any pure compounds. The crude material was chromatographed on silica. The only identifiable product was benzoic acid.

Method II. An alternative literature method[89] was adapted. o-Chlorophenol acetate was prepared in 98% yield by acetylation of o-chlorophenol in the usual way[109]. The product (18g.) was added to sodio-diethyl malonate (from diethyl malonate (17g.) and solid sodium hydroxide (4.5g.)) containing copper powder (1.8g.). The mixture was heated under reflux for 8 hours. Extraction with ether gave a brown oil (26g.) with a strong phenolic odour. The i.r. spectrum showed ν_{OH} at 3500 cm^{-1}. T.l.c. showed three spots, none of which corresponded to diethyl malonate. The crude reaction mixture was hydrolysed by heating under reflux for 3 hours in aqueous sodium hydroxide. The solution was acidified (concentrated hydrochloric acid) and heated under reflux for a further 4 hours. The reaction mixture was extracted with ether and separated into acidic and neutral fractions. Both of these were shown (t.l.c.) to be mixtures. One component in each fraction was identified (t.l.c.) as o-chlorophenol.

Attempted preparation of o-(carboxymethoxy)-phenylacetic acid(127)

Allyl phenyl ether was prepared and rearranged to o-allylphenol (in 96% yield) according to the standard method[90]. The i.r. spectrum of o-allylphenol showed vinyl double bond absorptions (ν max 1640, 1000 and 930 cm^{-1}).

The phenol was condensed with chloracetic acid by the method[60] previously used for the successful preparation of the acid (63). The product, a white solid, was recrystallised from water as fine needles, m.p. 145-147°. (Found: C, 68.69; H, 5.99. $C_{11}H_{12}O_3$ requires C, 68.73; H, 6.29%). The i.r. spectrum, however, did not correspond to that expected for o-allylphenoxyacetic acid (130). It showed broad hydroxyl absorption, and carbonyl absorptions at 1740 cm^{-1} (lactone) and 1705 cm^{-1} (aliphatic acid). The double bond absorption at 1640 cm^{-1} was very weak. Other bands occurred at 1380, 1240, 1125, 930, 760 and 700 cm^{-1}.

Attempted oxidation of the product from the above with alkaline permanganate gave only unchanged starting material.

Attempted periodate cleavage[110].

A solution of the supposed diol (80 mg.) in ethanol (4ml.)

was treated with a solution of sodium periodate (meta)(300mg.) in water (5 ml.) and the mixture warmed to homogeneity. It was allowed to stand overnight at room temperature, filtered and the filtrate evaporated to dryness under reduced pressure. The residue was washed with light petroleum and extracted with acetone. Concentration of the acetone solution gave a white semi-solid whose i.r. spectrum showed ν_{OH} 3500 cm^{-1}(m) and ν_{CO} 1725(s) and 1690 cm^{-1}; there was also a weak band at 2750 cm^{-1}. The material gave a 2:4-dinitrophenylhydrazone (m.p. (crude) ca. 90°) which decomposed to a brown oil on attempted recrystallisation. No bisulphite compound was obtained, but Fehling's solution was reduced.

The crude material from the above reaction was dissolved in warm water, made alkaline with solid potassium hydroxide and oxidised with aqueous potassium permanganate. The reaction mixture was worked up in the usual way to give an acidic product, a minute amount of a brown sticky oil whose i.r. spectrum showed hydroxyl absorption of the carboxylic acid type, and a broad unresolved carbonyl band. The oil could not be purified.

When the oxidation was carried out in acetone, the yield of material was extremely small and consisted of an intractable oil.

Attempted preparations of 4:5-dihydroxybenz-1-oxepin (122).

(a) Via homochroman-4:5-dione (132)

A solution of homochroman-5-one (65) (1.65g.; 0.01 mole) in ethanol (25 ml.) was heated to reflux temperature and a suspension of selenium dioxide (1.11g.; 0.01 mole) in ethanol (50 ml.) added. The mixture was heated under reflux for 1.5 hours, excess of ethanol distilled off, the residue taken up in ether, filtered, and extracted with cold 10% aqueous potassium hydroxide (3x). Acidification and extraction of the basic solution gave a brown oil whose i.r. spectrum showed broad hydroxyl (3500-3000 cm^{-1}) and carbonyl (1730-1680 cm^{-1}) absorptions. The oil gave a slow positive reaction with methanolic ferric chloride but failed to form a complex with nickel and hydroxylamine hydrochloride.

The crude product was treated with sodium borohydride and afforded a very low yield of a whiteish oil whose i.r. spectrum showed ν_{OH} at 3400 cm^{-1} and weak residual carbonyl absorption. Lack of material precluded any further investigation.

(b) Via 4-bromohomochroman-5-one (85).

The bromoketone (85) prepared as before (p.129) was heated under reflux for 5 hours in a suspension of silver oxide in water. The reaction mixture was filtered, extracted with ether and the ether extract concentrated to give a viscous yellow oil, ν_{OH} 3400-3300 cm^{-1}. The crude product (200 mg.) was dissolved in methanol and treated with sodium borohydride. During work up, a yellow solid was precipitated out and was removed by filtration. The filtrate was found (i.r.) to contain unchanged starting material. The yellow solid had an indefinite m.p. and proved impossible to recrystallise. The i.r. spectrum showed hydroxyl absorption (3500-3400 cm^{-1}) and weak carbonyl absorption. T.l.c. (5% methanol-chloroform) showed only one spot which did not, however, correspond to that given by the supposed diol (p.155).

(c) Via epoxidation of 2:3-dihydrobenz-1-oxepin (91).

A solution of the olefin (91) (1.152g.) in dry Analar chloroform was added dropwise, with shaking to a solution of perbenzoic acid[91] in chloroform (57 ml.; 0.15M), at 0°. The solution was kept at 0° until a negative reaction was obtained with moist starch-iodide paper (72 hours). The solution was stirred for 48 hours over solid calcium hydroxide containing anhydrous magnesium sulphate, but remained acid to litmus. It was therefore filtered and the filtrate washed with saturated sodium hydrogen carbonate, with brine, and dried. Removal of chloroform left a viscous cloudy oil (1.5g.) whose i.r. spectrum showed it to be a hydroxy-monobenzoate (133 or isomer). The i.r. spectrum showed ν max 3450, 1720, 1270, 770, and 720 cm^{-1}.

The hydroxy-monobenzoate was hydrolysed:-

(i) with sodium methoxide:- the hydroxy-monobenzoate (0.75g.) was heated under reflux for 5 hours in a solution of sodium methoxide in dry methanol. The solution was neutralised with gaseous carbon dioxide, excess of methanol removed under reduced pressure, the residue taken up in ether and filtered. Removal of the ether left a viscous oil shown (i.r.) to be unchanged starting material.

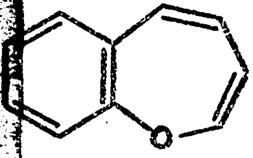
(ii) with methanolic potassium hydroxide:- a solution of the hydroxy-monobenzoate (0.75g.) in methanol (25 ml.) containing potassium hydroxide (0.17g.) was heated under reflux for 4 hours. Excess of methanol was removed under reduced pressure, the residue flooded with water, extracted with ether and the layers separated. The aqueous layer on acidification gave benzoic acid. The ether extract was washed (brine), dried and concentrated to give a whiteish sticky oil which could not be induced to solidify. The i.r. spectrum showed strong hydroxyl absorption (3400-3200 cm^{-1}) and complete absence of carbonyl absorption. The product was partially soluble in hot light petroleum.

Petroleum-soluble material:-

Concentration of the light petroleum extract gave an oily, low-melting solid which could not be recrystallised. The i.r. spectrum showed ν_{OH} at 3400 cm^{-1}. The crude material was heated under reflux for 3 hours with a mixture of acetic anhydride and dry pyridine. The reaction mixture was dissolved in ether, washed with dilute mineral acid, with brine and dried, Concentration of the ethereal solution gave a yellow oil which solidified on cooling. The solid was crystallised from ethyl acetate-light petroleum mixtures and then recrystallised from light petroleum as white needles, m.p. 100-103°. (Found: C, 63.72; H, 6.18. $C_{14}H_{16}O_5$ requires C, 63.62, H, 6.10%). On admixture with the presumed diacetate already examined (p. 155) the m.p. was depressed. The i.r. spectrum showed a single sharp carbonyl band at 1755 cm^{-1} and C - O absorption at 1245 cm^{-1}.

Petroleum-insoluble material.

The petroleum insoluble residue was taken up in ether and the solid reprecipitated by addition of light petroleum. The solid was identical (i.r., m.p.) with the supposed diol obtained previously (p. 155). Acetylation of the solid gave a crystalline diacetate, identical with that previously obtained (p. 155). On admixture with a sample of the diacetate m.p. 100-103° (see above), the m.p. was depressed.



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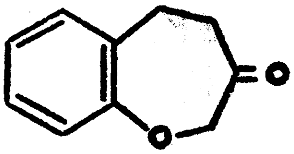

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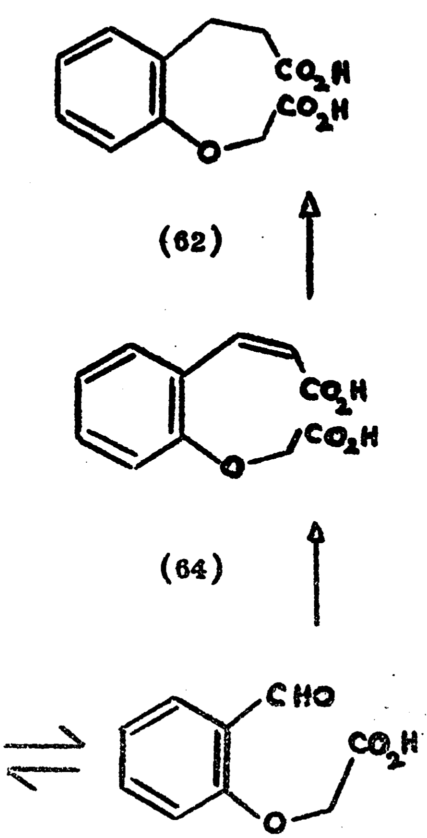

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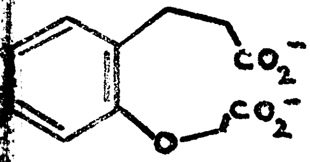

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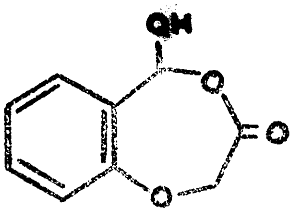

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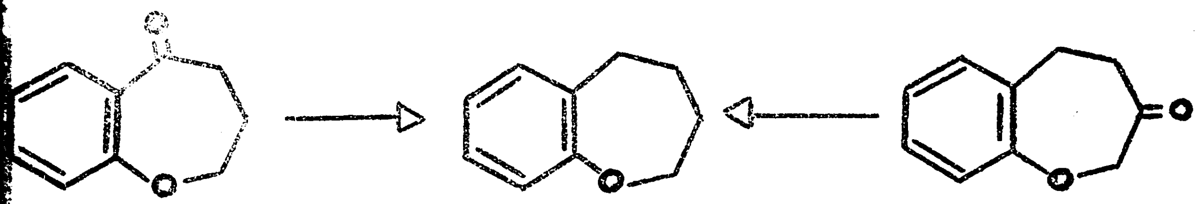

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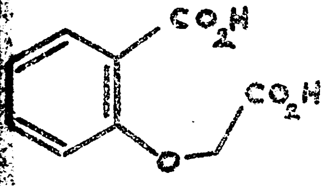

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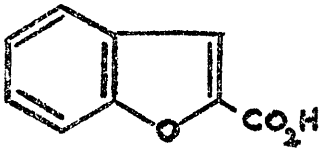

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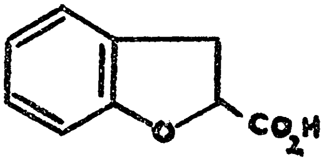

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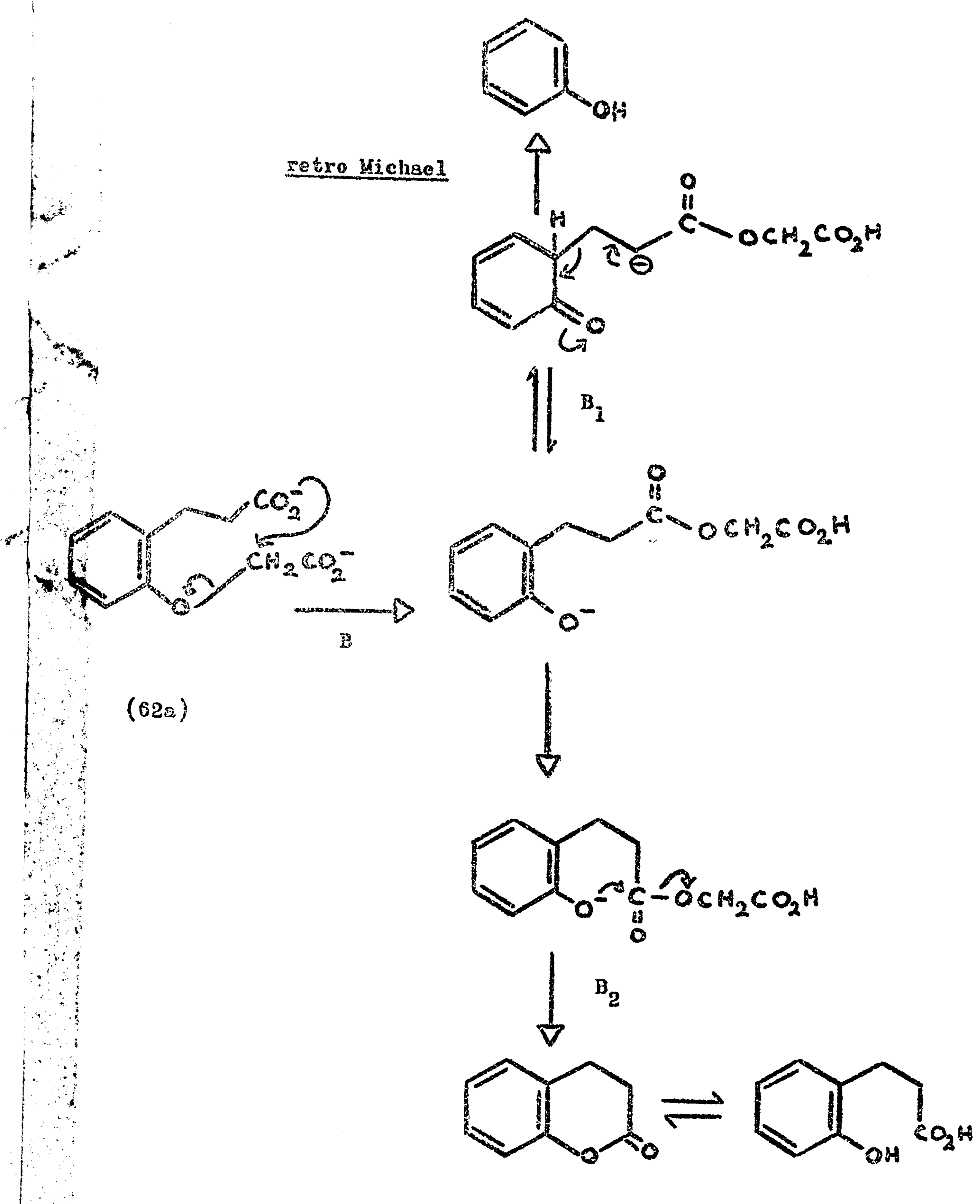
SCHEME B



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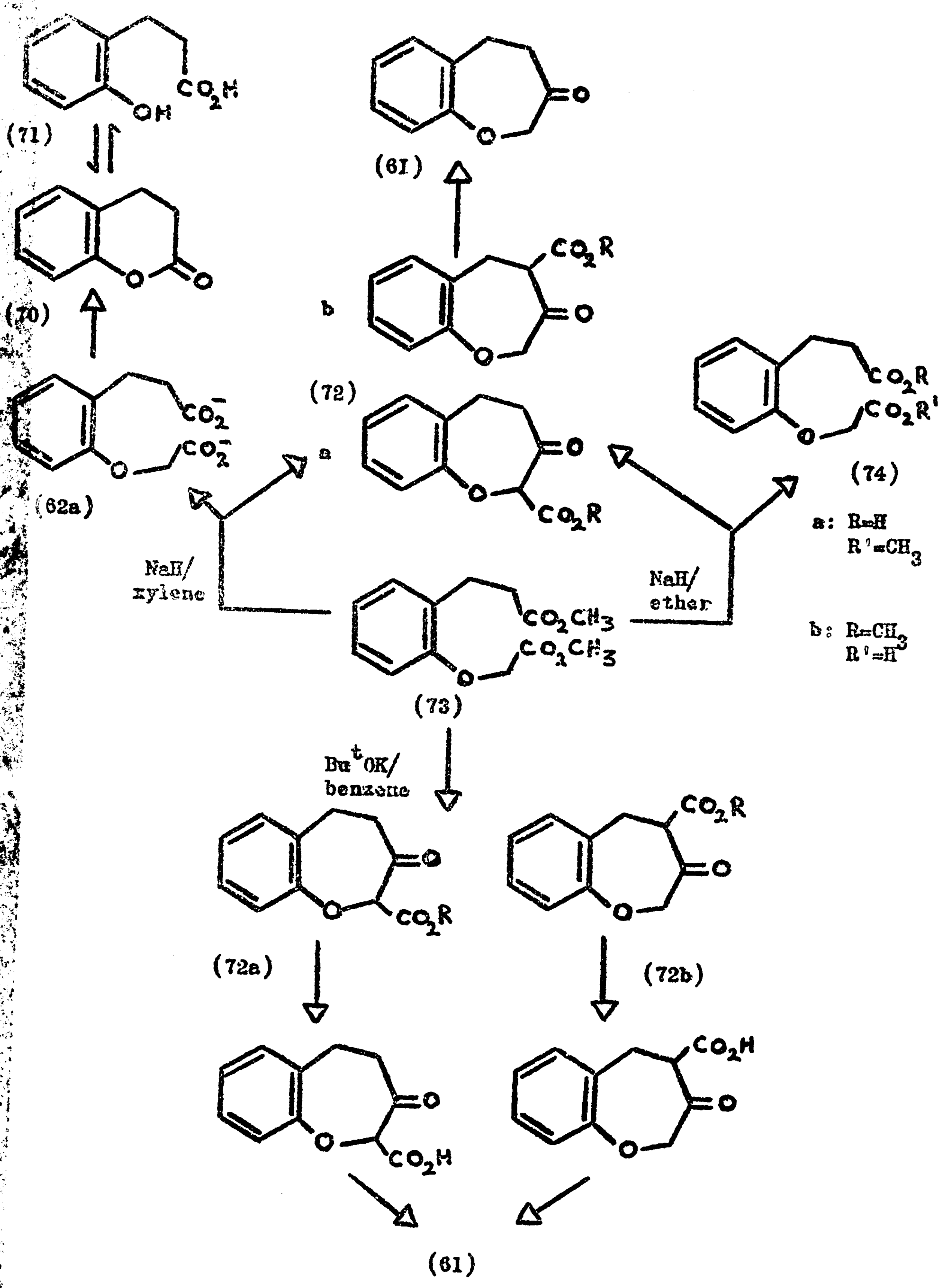

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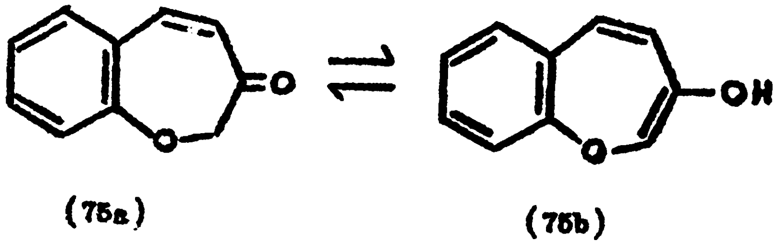
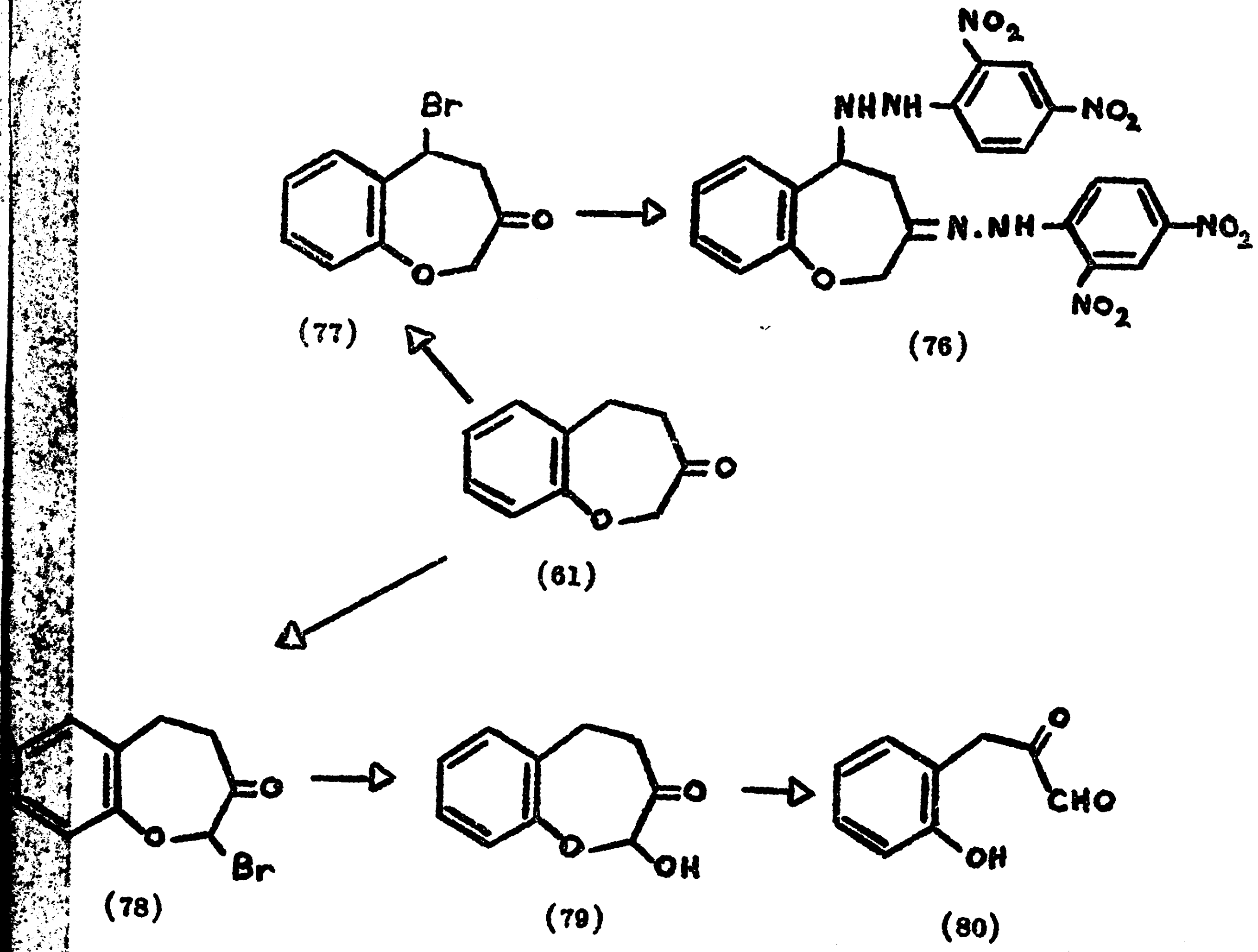
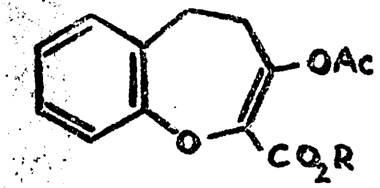
(74)
a: R=H
R'=CH$_3$
b: R=CH$_3$
R'=H
NaH/
xylene
NaH/
ether
(73)
Bu^{t}OK/
benzene
(72a)
(72b)
(61)


O
OH
(75a)
(75b)


Br
O
NO2
NHNH
NO2
N.NH
NO2
NO2
(77)
(76)
O
(61)
O
Br
(78)
O
OH
(79)
O
CHO
OH
(80)



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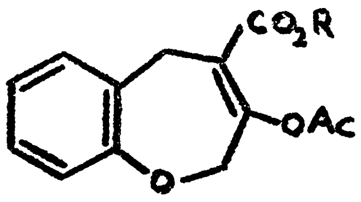

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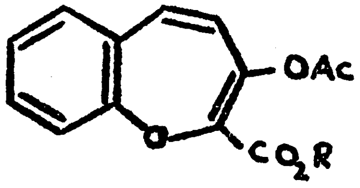

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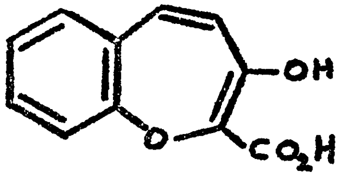

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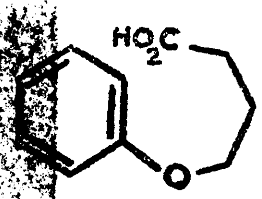

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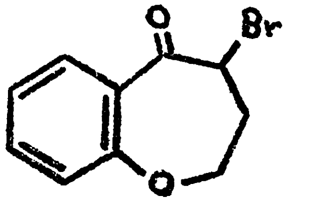

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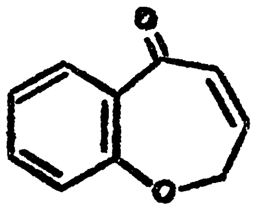

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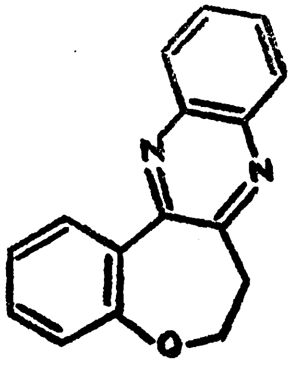

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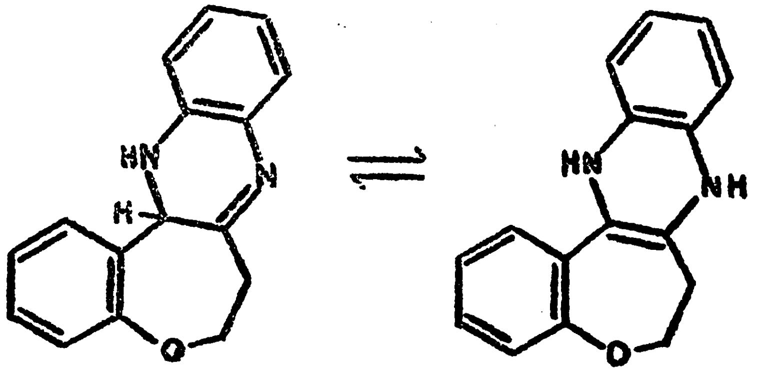

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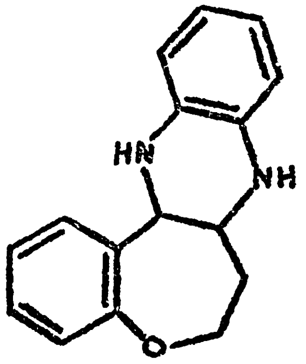

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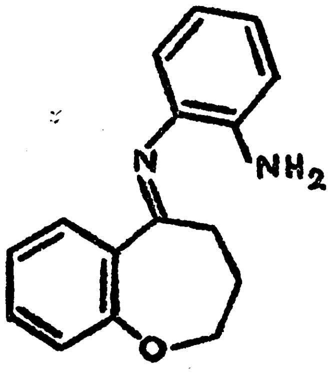

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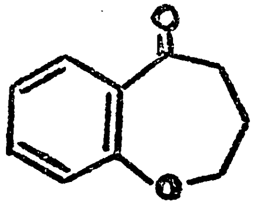

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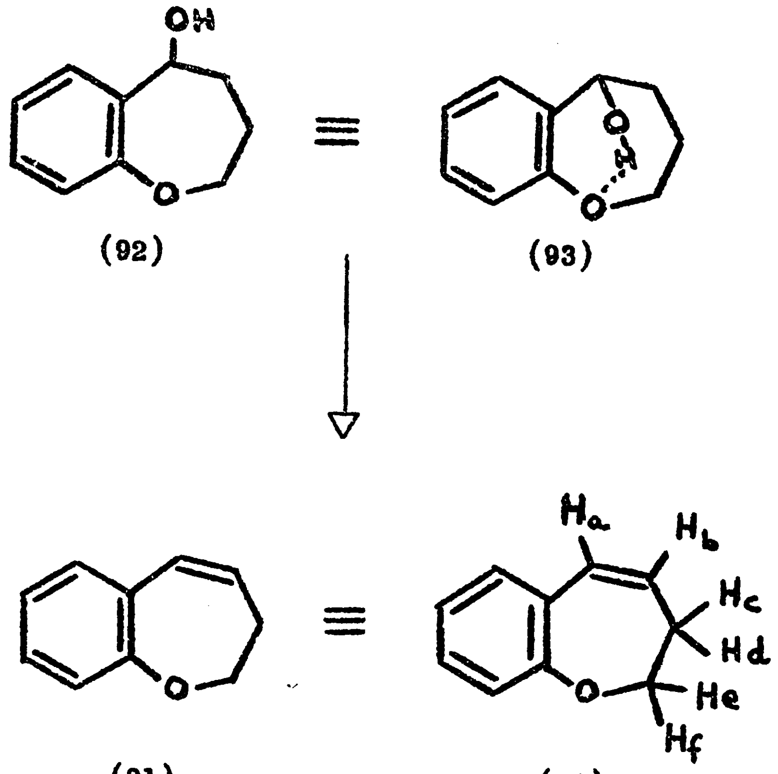

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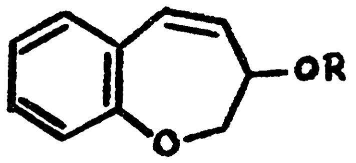
(91) (94)



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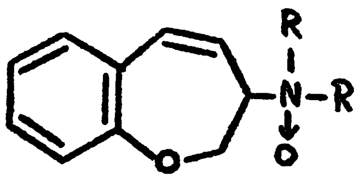

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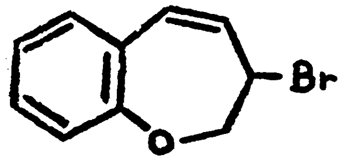
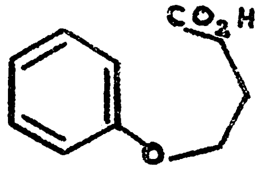


(112)

APPENDIX I



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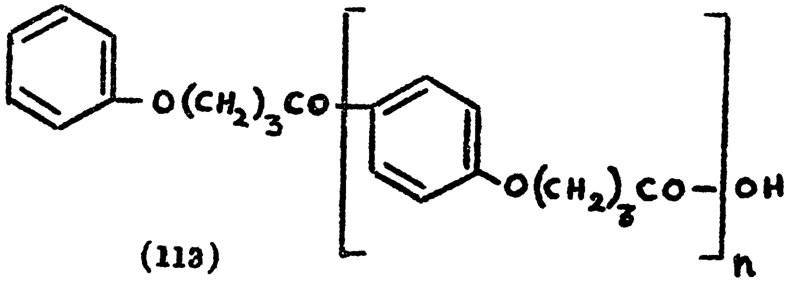

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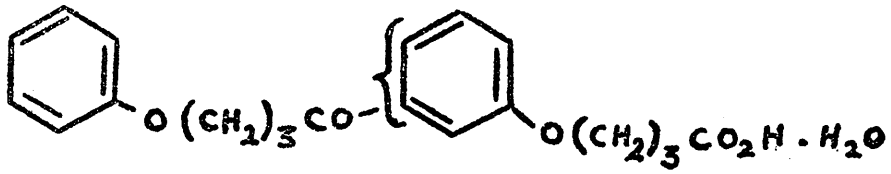

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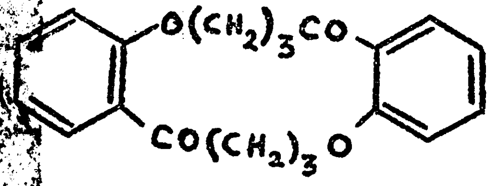

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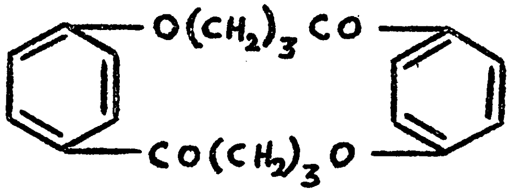

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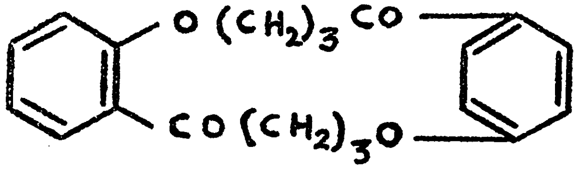

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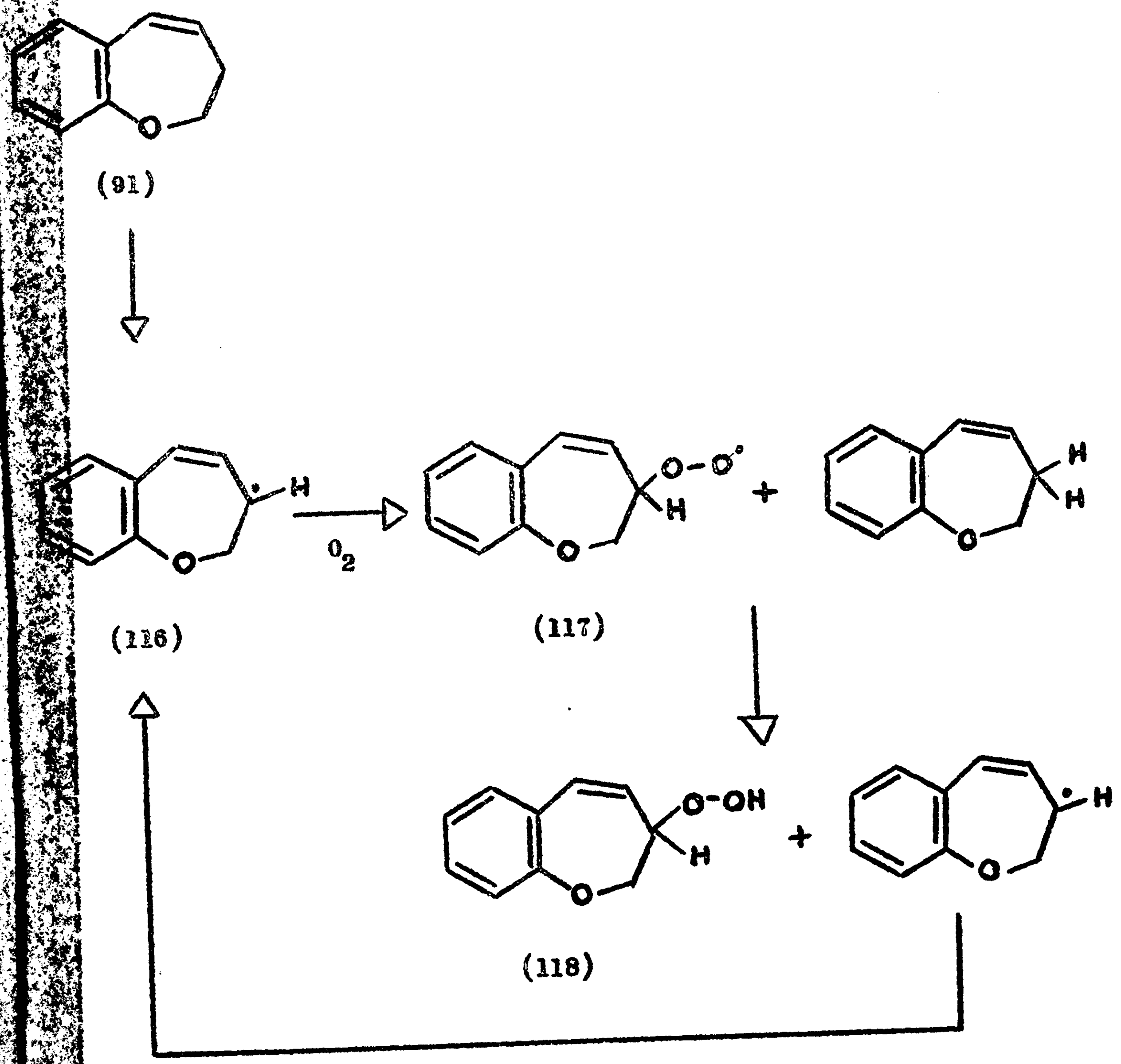
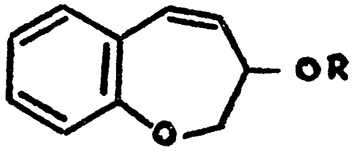
APPENDIX II

SCHEME C



APPENDIX III



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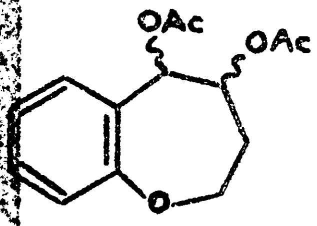

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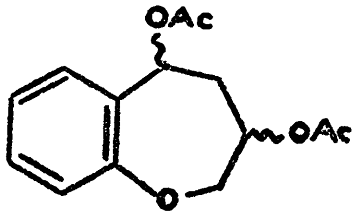

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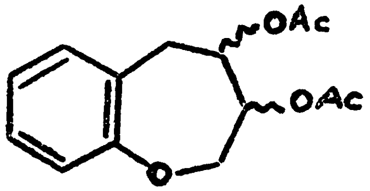

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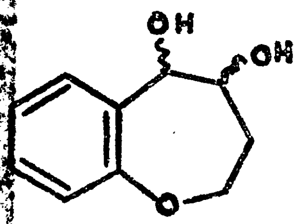

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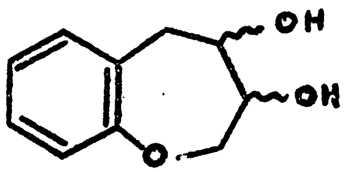
(122a): trans



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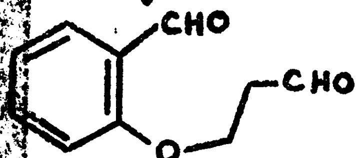

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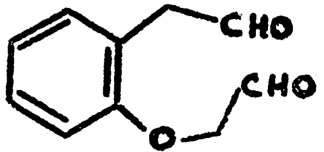

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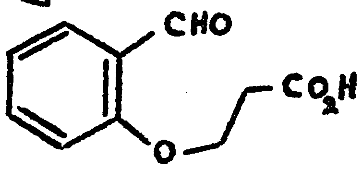

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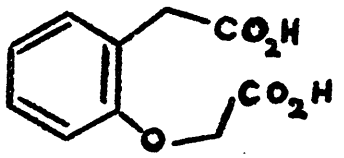

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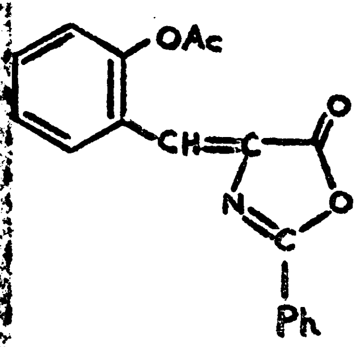

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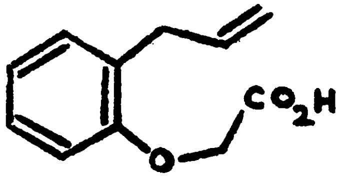

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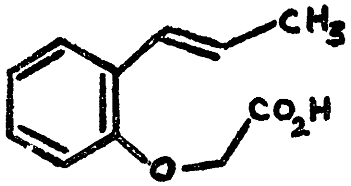

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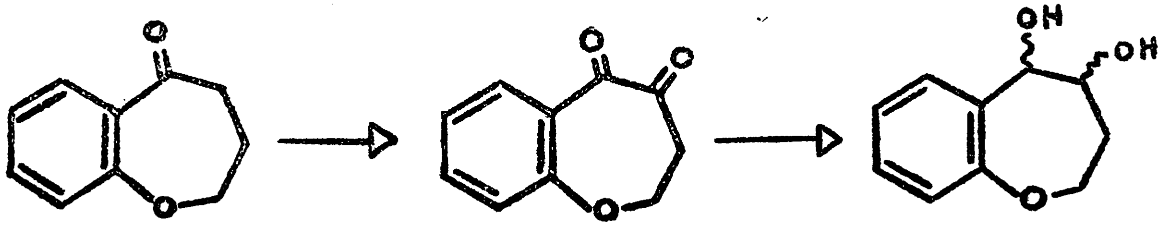

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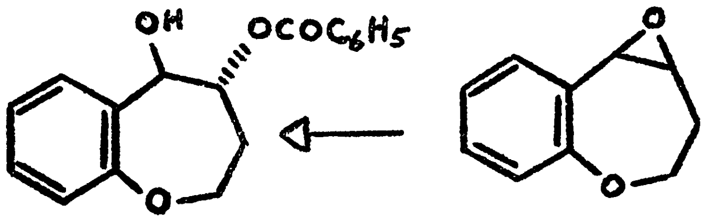

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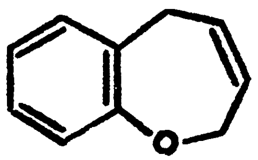


(135)

PART II

INTRODUCTION

Although a large number of synthetic methods to five- and six-membered rings are available, methods of synthesis of medium-sized rings are few, and so inflexible that means of placing substituents in a chosen position are fraught with difficulties. Any new method of synthesis, especially one in which substituents could be easily introduced, would therefore be of great importance.

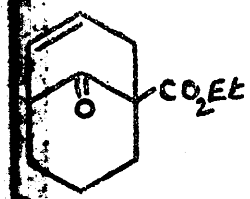
Recent publications from this department and elsewhere have been concerned with bridged bicyclic systems and some of these describe methods by which the bridge may be opened, giving rise to medium-sized ring systems.

Thus Cope[111] found that 1-ethoxycarbonylbicyclo-[3:3:1]-non-3-en-9-one (1) would undergo a reverse acetoacetic ester condensation, under the action of sodium ethoxide, to give 1:5-diethoxycarbonyl-cyclooöct-1-ene (2). Work has also been carried out by Buchanan, McKillop and Raphael[112] on the analogous 1-ethoxycarbonyl-5-methylbicyclo-[3:3:1]-non-3-en-9-one (3). This was expected to yield, on treatment with sodium ethoxide, 1-methyl-1:5-diethoxycarbonylcyclooöct-2-ene (4), concomitant shift of the double bond into conjugation with the ester carbonyl group being in this case prohibited. In actual fact the product was not the expected one, but a hydroxy-acid shown to be 5-methyl-9-hydroxy-bicyclo-[3:3:1]-non-3-en-1-carboxylic acid (5). Similarly, treatment of the corresponding methyl ester (6) with sodium methoxide under the same conditions gave the same hydroxy-acid. It was found in other attempts to open the bicyclic keto-ester (3) that treatment with potassium hydroxide in ethanol, or with sodamide in xylene gave, again, the hydroxy-acid (5), while treatment with potassium t-butoxide in t-butanol gave the hydroxy-t-butyl ester (7). It later became evident that not only must the reaction be carried out in a non-reducing medium but that the C_1 carbalkoxy residue must not contain any potential reducing agent. The t-butyl ester (7) on treatment with potassium t-butoxide in t-butanol did in fact undergo a reverse acetoacetic ester condensation to give the required cyclooctene di-t-butyl ester (8).

In the homologous bicyclo-[4:3:1]-decane system (9), the same authors[112] found that reverse acetoacetic ester reactions were impossible although the tosylate (10) on treatment with ethoxide afforded the cyclononene diester (11).

In each of the above cases, a suitable "handle" had been built into the system to facilitate the opening process. It was of interest to investigate cases where no such functional group was included.

The most readily prepared simple bicyclic system was 2-phenylbicyclo-[3:3:1]-non-2-en-9-one (12), available from cyclohexanone, and it was the object of this work to investigate the bridge opening of such compounds as (12) and its analogues (13) and (14).



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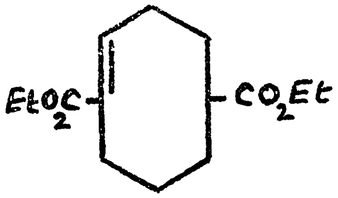

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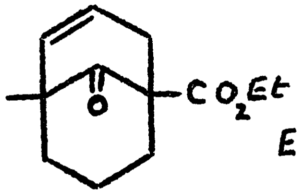

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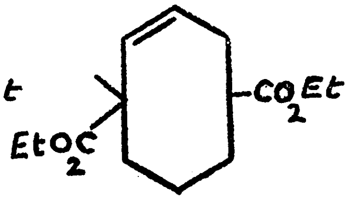

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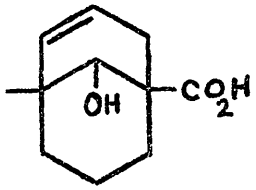

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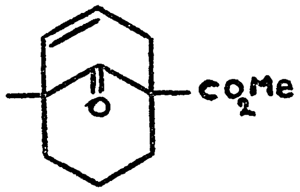

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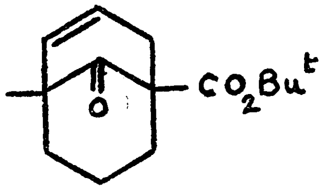

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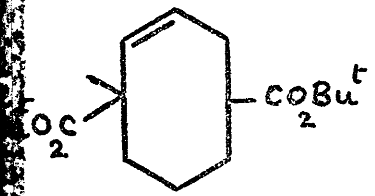

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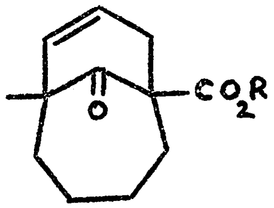

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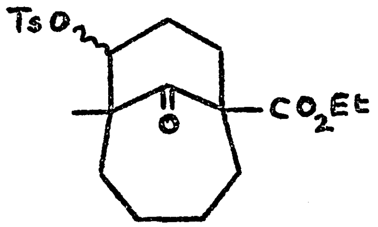

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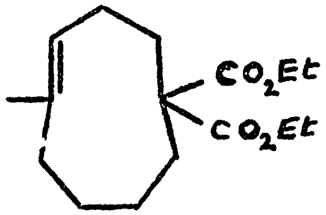

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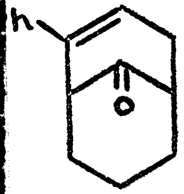

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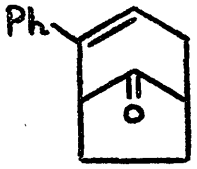

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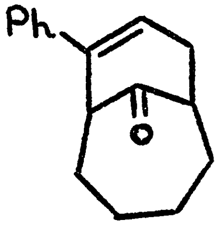

(14)

DISCUSSION.

The starting material for the preparation of the bicyclic ketones (12)-(14) whose ring-opening was to be investigated was, in each case, the appropriate 1:5-diketone (15), (16) or (17) .

It was found that these diketones could be prepared by two methods. 2- (β-Benzoylethyl)-cyclohexanone (15) and 2-(β-benzoylethyl)-cyclopentanone (16) were initially synthesised by the method previously used by Cope and Hermann[113] for the preparation of (15). This consisted essentially of a Michael reaction between the appropriate alicyclic ketone and phenyl vinyl ketone, liberated <u>in situ</u> from ββ'-dimethylaminopropiophenone (the Mannich base of acetophenone), present as its hydrochloride. The reaction was carried out in alkaline solution. Fractional distillation in each case afforded the required diketone as a low-melting solid, accompanied by a liquid by-product. These by-products, although not positively identified, were suspected (from i.r. spectra) of being the products of self-condensation of the starting materials, i.e. 2-(cyclopentylidene)-cyclopentanone (18) and 2-(cyclohexylidene)-cyclohexanone (19).

An alternative, and better, method for the preparation of the diketones was that applied by Gill and her co-workers[114] to the synthesis of the diketone (16). The diketones (15), (16), and (17) were obtained by heating the free Mannich base with the appropriate cyclic ketone (in a molar ratio of 1:3) at reflux temperature until all dimethylamine had been evolved. Excess of cycloalkanone was removed by distillation. The crude products were shown (t.l.c.) to be mixtures, but distillation at reduced pressure afforded the required diketones in a pure state. The diketones (15) and (16) were identical with those obtained by the first method; 2-(β-benzoylethyl)-cycloheptanone (17), not previously obtained, was also a low-melting solid, whose i.r. spectrum showed the two expected carbonyl absorptions, at 1702 and 1693 cm^{-1}.

The residues were not examined closely in the case of (15) and (17), but that from the preparation of (16) could be purified. The residue was a crystalline solid which analysed for the molecular formula $C_{23}H_{24}O_3$. The i.r. spectrum showed carbonyl absorptions at 1735 cm^{-1} (ring ketone) and 1692 cm^{-1} (aryl ketone). The compound was therefore assumed to be a di-addition product, from two molecules of phenyl vinyl ketone and one of cyclopentanone. The n.m.r. spectrum did not distinguish between the two possible isomers, 2:5-*bis* (benzoylethyl)-cyclopentanone (20) and 2:2-*bis* (benzoylethyl)-cyclopentanone (21). It is probable that the residues from the preparations of the other diones (15) and (17) contained the corresponding di-addition products. Attempts were later made to purify the crude diketones by simple recrystallisation but it was always found better to distil the products; the di-addition compounds appeared to be much higher-boiling than the required diketones and a more efficient separation could be achieved this way.

A slight modification to the literature method for the preparation of these diketones was found to improve both the purity and yield of the products. The reflux time for the reaction was shortened and residual dimethylamine neutralised with glacial acetic acid instead of being boiled off. This satisfactorily prevented any charring of the product through over-heating.

Since it was already known, it was decided to carry out experiments first of all on 2-phenylbicyclo-[3:3:1]-non-2-en-9-one (12). Following Cope and Hermann's method[113], the bicyclic ketone (12) was obtained by refluxing the diketone (15) in a mixture of glacial acetic acid and concentrated hydrochloric acid for 16 hours, to give the required ketone (12) as a low-melting solid . The i.r. spectrum (carbon tetrachloride) showed two carbonyl absorptions, instead of the expected single band. These occurred at 1732 cm^{-1} (ϵ 444) and 1722 cm^{-1} (ϵ 313). In chloroform the main band appeared at 1715 cm^{-1} (ϵ 437) with a small band at 1729 cm^{-1}

(ϵ 291) while in hexane carbonyl absorption occurred at 1736 cm^{-1} (ϵ 504) and 1724 cm^{-1} (shoulder, ϵ 160). If the two carbonyl absorptions were attributable to the presence of two different isomers, the intensities of the two bands would be expected to remain constant as the solvent varied; if the two absorptions were caused by two conformers, it would require a change of temperature to alter the relative intensities. The effect would therefore appear to be due to Fermi resonance. The n.m.r. spectrum (carbon tetrachloride) showed one olefinic proton at 3.8τ as a triplet (J = 4 cps). It was observed that on standing, the solid ketone became oily and the i.r. spectrum of this material showed hydroxyl absorption. Distillation of the oily material afforded again the solid ketone (12). This reversible reaction may be explained in terms of addition of the elements of water to the double bond of the ketone to give a hydroxy-compound which can be dehydrated on heating back to the ketone. The nature of this change was not further investigated. (Cope and Hermann[113] also noted that on standing the ketone (12) gave a gummy solid).

Since the purpose of this work was to try to open the diketone (12) (among others), to a medium-sized ring, a simple effective reagent which would permit this was sought. As previously mentioned (see Introduction) there was, in this case, no substituent group at the bridgehead which would assist the ring opening by direct attack of a reagent at the bridgehead carbonyl. It was thought likely, therefore, that an indirect attack would be more successful, and one way of achieving this was considered to be via the use of a peracid. Theoretically, treatment of the ketone (12) with a peracid could, by the Baeyer-Villiger reaction yield a lactone. Two isomers (22) and (23) are possible and it would be interesting to see which of these would be obtained. Both lactones (22) and (23) would of course open with base. It was also possible that epoxidation of the double bond would take place; the epoxy-ketone (24) depending on **its** stereochemistry could then be opened with either acid or base to give a substituted seven-membered ring (25).

The ketone (12) was accordingly treated with perbenzoic acid and with a mixture of peracetic acid and sodium acetate but yielded in both cases only unchanged starting material. Treatment with trifluoroperacetic acid likewise proved a signal failure and yielded only a glass which could neither be purified nor identified.

While this work was in progress, cyclisation reactions were being carried out on the diketones (16) and (17). Treatment of 2-(β-benzoylethyl)-cycloheptanone (17) with glacial acetic acid and concentrated **hydrochloric** acid gave the bicyclic ketone, 7-phenylbicyclo-[4:3:1]-dec-7-en-10-one

(14) as an oil which proved difficult to crystallise (it was later found (see p. 187) that a more satisfactory method of obtaining the ketone (14) was by cyclisation of the diketone (17) under the agency of p-toluene-sulphonic acid in dry benzene, with the removal of the water formed in the necessary aldol condensation. The products obtained by the two cyclisation methods were, however, identical). The ketone was initially crystallised from hexane-light petroleum mixtures as a white solid, m.p. 40°. On standing in the cold, the m.p. of this solid, in the dry state, rose to 78-80°. A sample of this higher-melting material on recrystallisation from light petroleum, gave a white crystalline solid m.p. 40°. Since the two materials possessed identical i.r. spectra and identical R_f values, it was assumed that the ketone (14) was dimorphic. The i.r. spectrum (carbon tetrachloride) showed the main carbonyl absorption band at 1718 cm^{-1} (ϵ 474) accompanied by a shoulder at 1710 cm^{-1} (ϵ 248). On further investigation it was found that in chloroform, the main band appeared at 1705 cm^{-1} (ϵ 350) with a shoulder ca. 1715 cm^{-1} (ϵ 222) while in hexane, the main band was at 1725 cm^{-1} (ϵ252) with a slight shoulder at 1710 cm^{-1} (ϵ 95). These results correspond to those observed for the analogous bicyclic ketone (12), and it is assumed that the same effect is operating. The observed carbonyl frequencies and intensities

TABLE I - Carbonyl Absorption Frequencies of the Bicyclic Ketones (12) and (14).

	(12)		(14)	
Solvent	ν(cm.$^{-1}$)	ν(cm.$^{-1}$)	ν(cm.$^{-1}$)	ν(cm.$^{-1}$)
Hexane	1736 (504)	1724 (160)	1725 (252)	1710 (95)
CCl_4	1732 (444)	1722 (313)	1718 (474)	1710 (248)
$CHCl_3$	1729 (291)	1715 (437)	1715 (222)	1705 (350)

Figures in parentheses are ε values.

of the two ketones (12) and (14) are listed in Table I.

The n.m.r. spectrum showed one olefinic proton as a poorly resolved triplet, at 3.98τ, (J = 4 cps). On treatment with an acidic solution of 2:4-dinitrophenylhydrazine, the ketone (14) gave a yellow derivative which was unstable to heat but could be obtained in a crystalline state by careful recrystallisation from large volumes of ethanol.

Attempted cyclisation of the diketone (16) under the same acidic conditions did not give the expected bicyclic ketone (13). Instead, a mixture of an acidic and a neutral material was obtained. The result was sufficiently unusual to merit a detailed study. It was also observed that alteration of the reaction time altered the ratio of acidic: neutral material in the product. Heating the diketone (16) under reflux with glacial acetic acid and hydrochloric acid for 8 hours gave a ratio of acidic:neutral material = 86%:14%, while a reflux time of 48 hours gave a ratio of acidic:neutral products = 30%:70%.

The Acidic Component.

The acidic material was a yellow viscous oil, b.p. 150-154°/0.15-0.2 mm. which, on cooling, became a glass, but could not be induced to crystallise. Microanalysis indicated a molecular formula of $C_{14}H_{16}O_2$ for the compound. The presence of a carboxyl function was established by solubility in aqueous sodium hydroxide and in aqueous sodium hydrogen carbonate, by ester formation on treatment with diazomethane, and from i.r. data. The i.r. spectrum (carbon tetrachloride) showed absorptions typical of a carboxylic acid. Hydroxyl absorption occurred at 3544-3518 cm^{-1} (ϵ, 46; $\Delta\nu_{\frac{1}{2}}$, 26 cm^{-1}) and carbonyl absorption at 1756 cm^{-1} (monomer; ϵ, 194; $\Delta\nu_{\frac{1}{2}}$, 17 cm^{-1}) and 1707 cm^{-1} (dimer, ϵ, 563; $\Delta\nu_{\frac{1}{2}}$, 14 cm^{-1}). On esterification, a single carbonyl absorption was observed at 1730 cm^{-1}, and there was complete absence of hydroxyl absorption.

The u.v. spectrum showed the presence of a styrene chromophone (λ max 250 $m\mu$; log ϵ, 3.98). This may be compared with the absorptions of styrene itself (λmax 248 $m\mu$; log ϵ, 4.15) of ω-methyl-styrene (26) (λ max 245 $m\mu$; log ϵ , 4.1)[115] and of α-methyl-styrene (27) (λ max 243 $m\mu$; log ϵ , 4.05)[116]. The unknown compound rapidly decolourised alkaline potassium permanganate. The presence of one double bond in the molecule was confirmed by the uptake of 1 molar equivalent of hydrogen, on catalytic reduction over 5% palladium-charcoal. The product, a white crystalline solid, m.p. 57°, did not decolourise permanganate and its u.v. spectrum showed only benzenoid absorption.

The i.r. spectra of both the saturated and unsaturated acids showed the presence of a mono-substituted benzene ring.

(ν max 756 and 690 cm^{-1}). Assuming (from ϵ values and molecular formula) the presence of only one carboxyl group, there then remained seven carbon atoms whose relation to each other had to be established. That these carbon atoms constituted a seven-membered ring was shown as follows. Decarboxylation of the unsaturated acid was attempted by a number of methods. Distillation of the acid from soda-lime and treatment with copper powder and quinoline both gave unchanged starting material. Refluxing the acid in diphenyl ether gave unchanged starting material accompanied by a neutral fraction which was shown (t.l.c.) to contain eleven components. None of these has so far been identified. The reduced acid, however, on refluxing under nitrogen for 72 hours in quinoline, containing copper powder, has been found by Mr. Henderson[117] to yield an oil (3%) identified as phenylcycloheptane. The product was identical with an authentic sample of phenylcycloheptane with respect to i.r. and n.m.r. spectra.

The structure of the unknown acid may then be written as (28) with the position of the carboxyl group so far unspecified. At this point it was helpful to consider a possible mechanism by which a phenylcycloheptene acid could be formed during the reaction and it seemed necessary to invoke a bicyclic intermediate. If it were assumed that the diketone (16) did in fact give the bicyclic ketone (13), it is possible to postulate an acid catalysed ring-opening of (13) to give the phenylcycloheptene acid (29) (Scheme A_1). Another possibility is that the ring-opening proceeds via a ketene intermediate (30) as shown (Scheme A_2). This would give rise to the same unsaturated acid (29), so that either of these mechanisms suggests a possible location for the double bond.

Accordingly, oxidative experiments designed to cleave the ring system at the double bond were undertaken to establish the relative positions of the double bond and the carboxyl group.

Treatment of an alkaline solution of the unknown acid with saturated aqueous potassium permanganate gave a water-soluble white crystalline solid, m.p. 118-122°. This was identified by comparison with an authentic sample as simply benzoic acid, whose presence may be readily explained on the basis that oxidation had taken place at the double bond to one end of which the phenyl group was attached, but had proceeded further than was hoped for.

The oxidation was then carried out in neutral acetone solution, to give an oily product which was shown by t.l.c. to be a mixture of several compounds. These were separated, by extraction, into acidic and neutral fractions. The acidic material was found to be unchanged starting acid.

The neutral fraction was examined by t.l.c. and contained between eight and ten compounds narrowly separated from each other. Several of these were shown, by use of appropriate staining agents, to contain carbonyl compounds, but the mixture could not be separated. Oxidation of the unknown acid by potassium permanganate was therefore abandoned, and an alternative ring-cleavage by ozonolysis was investigated.

The ozonolysis was carried out in methylene chloride at -70° and the ozonide worked up in two different ways. Ozonides may be decomposed either reductively, to give, in this case, a keto-aldehyde, or oxidatively, to give, in this particular case, a keto-acid. A reductive work-up was chosen initially, and the crude ozonide was stirred with powdered zinc and acetic acid until a negative starch-iodide test indicated that the ozonide had been completely decomposed. Filtration and evaporation of the solvent left the product as a yellow oil which contained a white solid. The oil could not be induced to crystallise nor did trituration effect any separation of the solid and liquid components. The i.r. spectrum of the crude material showed hydroxyl absorption and a broad, poorly resolved carbonyl band, which did, however, indicate three separate absorptions (ca. 1740, 1715, 1680 cm^{-1}). It was decided not to proceed with the purification of this material but to oxidise it in the crude state converting any aldehydic material present into the corresponding acidic compound. The crude product was oxidised with Jones's reagent[84] in the usual way to give a yellow semi-solid mass from which a white crystalline solid could be precipitated by addition of small amounts of acetone. The solid was removed and examined separately. The residue was shown by t.l.c. to contain three compounds, all of which were strongly adsorbed near the origin, and could not be separated by chromatography. The i.r. spectrum of the mixture gave no indication of the nature of the components, showing only acidic hydroxyl absorption and broad, unresolved carbonyl absorption. This residue was not therefore examined further.

The solid previously removed from the crude reaction product melted over a considerable range of temperature. Extreme insolubility in most organic solvents rendered it unsuitable for purification by recrystallisation, while strong adsorption on both silica and alumina prohibited purification by chromatography. Apart from hydroxylic absorption, the i.r. spectrum showed carbonyl absorptions at 1725(sh), 1715, 1685, and 1675 cm^{-1}. This, and the indefinite m.p. indicated that the solid was probably a mixture. Apart from the possibility of there being more than one product obtained from ozonolysis, oxidation by Jones's reagent may not have gone to completion.

This attempt was therefore discarded and the ozonolysis repeated, using this time an oxidative work-up which was expected to yield a keto-diacid. The ozonide, prepared as previously, was decomposed by adding it to a warm solution of 30% hydrogen peroxide and heating the mixture under reflux until decomposition was complete. The crude product, a semi-solid was shown by t.l.c. to be a mixture of six compounds. The crude mass was dissolved in ether and the ethereal solution washed with aqueous ferrous sulphate with the intention of removing any excess peroxide present. Instantly, however, a brown curdy precipitate was obtained and it was found that part of the product had complexed with ferrous sulphate. The complex could be decomposed on acidification and gave a white solid, identical with the acidic material obtained by base extraction of the ethereal solution. The solid did not have a sharp m.p. (165-170°) but repeated washing with ether gave purer material. This was at first thought to be one compound since t.l.c. (15% ethyl acetate-light petroleum) showed only one spot. Closer examination by t.l.c. (benzene-dioxan-acetic acid; 90:25:4 by volume) revealed, however, that three compounds were present, two of them in very small amounts. High insolubility rendered recrystallisation impossible. The i.r. spectrum of the slightly impure material showed strong carbonyl absorption at 1702 cm^{-1} and weaker absorption at 1692 cm^{-1}.

An orange 2:4-dinitrophenylhydrazone was obtained only in highly concentrated solution, the derivative being extremely soluble in methanol.

It was hoped that esterification of the acidic material would render it easier to purify. Treatment with diazomethane gave an ester whose i.r. spectrum showed carbonyl absorptions at 1730 cm^{-1} (ester) and 1690 cm^{-1} (aryl ketone). T.l.c. of the oil showed three spots. Distillation did not effect any separation of the mixture. Similarly, an attempted separation by thick-plate chromatography proved unsuccessful.

Treatment of the crude acidic material with acetyl chloride gave a crystalline keto-anhydride, of molecular formula $C_{14}H_{14}O_4$. The i.r. spectrum (in carbon tetrachloride) showed carbonyl absorptions at 1863 and 1794 cm^{-1} (anhydride) and 1692 cm^{-1} (aryl ketone). Contrary to expectations, the anhydride bands were those of a typical succinic anhydride (succinic anhydride[118] itself shows carbonyl absorptions at 1865 and 1782 cm^{-1}) and not those of a substituted glutaric anhydride (glutaric anhydride[118] shows carbonyl absorptions at 1802 and 1761 cm^{-1}). This would imply that the structure of the anhydride obtained was (32) and not that expected (33). The n.m.r. spectrum (deuterochloroform) neither confirmed nor contradicted the infra-red evidence, showing only a broad band in the region of 6.9 τ given by five protons adjacent to carbonyl groups and another unresolved band ca. 8.1τ, attributed to four methylene protons. Either of the structures (32) or (33) would give such a result.

The keto-diacid corresponding to the anhydride obtained must therefore have the structure (34). This, in turn, could only have arisen from ozonolysis of the phenylcycloheptene acid (35), i.e. 4-phenylcyclohept-3-ene carboxylic acid, and not from the acid previously postulated, (i.e. 4-phenylcyclohept-4-ene carboxylic acid (29)) as being the product of ring-opening of the bicyclic ketone (13) under acid conditions.

These findings raised some doubts about the validity of the mechanisms proposed for the ring opening (p. 178). Neither of these was acceptable, unless it were assumed that the acid (29) was first obtained (as suggested by both mechanisms) and then isomerised under acid catalysis to the other acid (35). Such an isomerisation could occur readily but there appeared to be no driving force which would cause it to take place. A study of molecular models did not indicate any stereochemical or conformational advantage to be gained by isomerisation of the double bond. Obviously further investigation into the mechanism of the ring-opening was necessary. The first question to be settled was whether the bicyclic ketone (13) was in fact the true intermediate or not.

Work was consequently begun to prepare and isolate the

TABLE II. ATTEMPTED CYCLISATIONS OF THE DIKETONE (16).

				REACTION PRODUCTS *				
REAGENT	Wt. of (16)	Temp.	Time.	(16)	(13)	(29),(35)	(40)	OTHERS
(a) c.HCl/HOAc	37 g.	Reflux	48 hr.	-	-	+	+	-
(b) c.HCl/HOAc	37 g.	Reflux	8 hr.	-	-	+	+	-
(c) c.HCl/HOAc/Na_2SO_3	10.8 g.	Reflux	8 hr.	+	-	+	+	-
(d) c. H_2SO_4	5 g.	20°	24 hr.	+	-	-	-	-
(e) Dil. HCl/dioxan	4 g.	80°	3 hr.	+	-	-	-	-
(f) $HClO_4$/dioxan	1 g.	20°	48 hr.	+	-	-	-	-
		Reflux	2 hr.	+	-	+	-	-
(g) NaOMe/MeOH	0.13 g.	20°	24 hr.	+	-	-	-	-
	0.21 g.	Reflux	2 hr.	+	-	Trace	-	-
(h) HCl(g)/EtOH	10.8 g.	Reflux	2 hr.	-	-	+	-	+
(i) HCl(g)/CCl_4	2 g.	Reflux	3 hr.	+	-	-	-	-
(j) HCl(g)/Bu^tOH	2 g.	Reflux	3 hr.	+	-	-	-	-
(k) HCl(g)/dioxan.	5 g.	Reflux	1.5 hr.	+	-	+	-	-
(l) BF_3/C_6H_6	0.5 g.	5°	1 hr.	+	-	-	-	-
	0.5 g.	20°	24 hr.	+	-	-	-	-
	20 g.	Reflux	3 hr.	-	+	+	-	(20) or (21)

* (40) ≡ lactone

elusive bicyclic ketone (13). Many attempts were made under a large variety of conditions to prepare this ketone, the effort being eventually rewarded by a successful synthesis. The cyclisation conditions which were studied are tabulated (Table II)* for convenience.

On the assumption that the bicyclic ketone (13) was in fact the precurser of the acidic material obtained and that the system (13) itself was unstable to acid, it was first thought that the presence of a reducing agent in the cyclisation medium would prove advantageous. Preferential reduction of the carbonyl group of (13) would preserve the bicyclic system in a reduced form and render it less susceptible to ring opening. Sodium sulphite (as a one-electron reducing agent) was therefore added to the reaction mixture (acetic acid and hydrochloric acid) but the only products were the acid (35) and the neutral material (lactone, see * and p.192) previously obtained.

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* In Table II, "lactone" refers to the neutral material originally recovered from acid treatment of the diketone (16) (p. 175) and whose structure was subsequently proved (p. 194). Assumption of the nature of this particular compound before proof of its structure is given is necessary to avoid confusion with other "neutral material" obtained in the cyclisations.

Other acidic cyclisation reagents (sulphuric, hydrochloric and perchloric acids) did not promote any reaction at all, and the starting diketone (16) was returned unchanged. Basic conditions (sodium methoxide in methanol) gave similar results. It seemed likely that an aqueous medium was unsuitable for the reaction and cyclisation conditions in non-aqueous media were therefore investigated. Gaseous hydrogen chloride was used as cyclisation agent in a number of solvents. In carbon tetrachloride and dry _t_-butanol the starting material was returned unchanged. With dioxan as solvent, the product consisted mainly of unchanged starting material but a small amount of the acid (35) was also recovered, along with a negligible amount of another neutral material which could have been identical with the neutral material originally obtained (see p. 175) but was not positively identified. With dry ethanol as solvent for the gaseous hydrogen chloride, no starting diketone was recovered. The product was separated into acidic and neutral components. The former was shown (i.r., t.l.c.) to be the acid previously obtained. It was present in almost negligible amounts. The neutral material, a yellow oil, was obtained in over 70% yield. T.l.c. showed it to be a mixture of three compounds which were separated by chromatography on alumina. Elution with 5% ethyl acetate-light petroleum gave a mobile oil with an ester-like odour.

The i.r. spectrum showed a single sharp carbonyl band at 1740 cm^{-1} and strong absorption in the 1250 cm^{-1} region. Hydrolysis of this material with alcoholic potassium hydroxide gave a yellow viscous oil identified as the acid (35). This fraction from the chromatographic separation was thus presumed to be the ethyl ester of the acid (35). Elution with 10% ethyl acetate-light petroleum afforded the second fraction, a white crystalline solid, m.p. 99-104°, identified (i.r. and t.l.c.) as the di-addition product (20) or (21) . The third fraction was eluted with 20% ethyl acetate-light petroleum as a yellow oil which was shown to be a mixture of the di-addition product and another material which could not be identified. The i.r. spectrum showed that it contained both hydroxyl and carbonyl functions.

Cyclisation was next attempted using boron trifluoride etherate in dry benzene, at various temperatures. The results were as shown in Table II. One set of conditions did yield a material which from later work (p. 188) was identified as the required bicyclic ketone (13), although in poor yield and in an impure state. The reaction afforded both acidic and neutral materials (in a ratio of 30%:70%). The acidic material was identified as the acid (35). The neutral material was shown by t.l.c. to consist of two main compounds, R_f = 0.54 and 0.23 respectively (R_f for starting diketone(16)

= 0.31). Chromatography of this neutral material on alumina (grade I, neutral) appeared to cause severe decomposition and several materials were recovered from the column. Among these was a colourless oil (27% of the total) which solidified on standing. The material had the same m.p. as the starting diketone (16) but depression of m.p. was observed. Successful recrystallisation of the material was not achieved, the product always being obtained as an oil, indicating that it was of low purity. The i.r. spectrum showed a single carbonyl absorption (ca. 1760 cm^{-1}) and from this, it was later identified as the desired bicyclic ketone (13). Approximately 16% of the material recovered from the column was the di-addition product (20) or (21) while the remaining 50% was shown (i.r. and t.l.c.) to be the acid (35). The overall yield of bicyclic ketone (13) by this method was only 16.5% and, as shown, even this was not obtained in a pure state.

The indications, at this point, being that an anhydrous medium was essential for the isolation of the bicyclic ketone (13), the cyclisation was finally carried out under conditions in which even the water formed in the aldol condensation itself was removed. The diketone (16) was refluxed in dry benzene containing p-toluenesulphonic acid, removing any water formed by means of a Dean and Stark water separator[119]. The reaction was worked up by neutralising the reagent with solid potassium carbonate mixed with a small amount of anhydrous magnesium sulphate. Filtration, followed by removal of the benzene gave the product as a brown oil shown by t.l.c. to be a mixture of three compounds. Chromatography of the product on silica, as in the case of the boron trifluoride product (see p. 187) occasioned decomposition and the number of materials eluted from the column was considerably greater than three (see Experimental). Among these, however, it was possible to identify three major components. The first material isolated (1.2% of the total) was a yellow oil, with an ester-like odour, shown (t.l.c.) to be a pure compound. The i.r. spectrum showed a single carbonyl band at 1738 cm^{-1}. Although lack of material prevented identification of this compound it was supected of being a p-toluenesulphonate ester.

The bicyclic ketone (13) was then eluted (68% of the total), followed by a mixture of fine compounds, one of which was identified as the starting material (16).

The bicyclic ketone itself (13) was obtained in 52.8% yield by this method. It was recrystallised from a mixture of benzene and light petroleum as white needles, which consistently showed two m.p.'s:- 71-75° and 89-93°. The i.r. spectrum (carbon tetrachloride) showed a single carbonyl absorption at 1758 cm^{-1} (ϵ, 548) accompanied by three small bands at

TABLE III. REACTIONS OF THE BICYCLIC KETONE (13)

REAGENT.	REFLUX TIME	Wt. of (13)	REACTION PRODUCTS	
			Acid (29), (35).	Neutral *.
c.H_2SO_4 / Dioxan	2.5 hr.	228 mg.	50 mg.	162 mg. L
NaOH / Dioxan	2.5 hr.	142 mg.	50 mg.	10 mg. L or D
Water / Dioxan	2.5 hr.	267 mg.	75.4 mg.	127 mg.
c.HCl / HOAc	2.5 hr.	69.5 mg.	20 mg.	20 mg.
Water	3.3 hr.	81.8 mg.	50 mg.	4 mg.

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* L signifies lactone (40) present in neutral material.

D signifies diketone (16) present in neutral material.

3085, 3064 and 3030 cm^{-1} (ϵ, 22.6; 28.3; 39.6 respectively). The n.m.r. spectrum showed a single olefinic proton at 4.1 τ as a triplet (J = 3.75 cps).

The bicyclic ketone gave a yellow 2:4-dinitrophenylhydrazone, yellow needles, m.p. 70-73°. On reduction, over 5% palladium-charcoal, the ketone (13) was observed to take up 1 molar equivalent of hydrogen to give a colourless oil which could not be induced to solidify. The oil showed carbonyl absorption ca. 1735 cm^{-1} (i.e. at lower frequency than the bicyclic ketone (13)). A yellow 2:4-dinitrophenylhydrazone was obtained, m.p. 72-75° which on admixture with the corresponding derivative of the bicyclic ketone showed a depression of the m.p.

Reduction of the bicyclic ketone with sodium borohydride gave a mixture of products. One of these was identified (t.l.c.) as the diketone (16), while the other was of unknown constitution; the mixture could not be separated.

The bicyclic ketone was refluxed in a series of acidic, basic and neutral media (see Table III). In every case, acidic material identified as the acid (35) was obtained. It was noted especially that the presence of water alone was sufficient to cause ring-opening of the bicyclic ketone.

Since it was now established that the bicyclic ketone (13) was indeed the precursor of the acid (35), both the mechanisms proposed for ring opening (p. 178) hold good if, as previously suggested the initial product was the acid (29), which could readily isomerise to (35). Later work (p. 203) did in fact suggest that an equilibrium was set up between the two acids and that both were present in any acidic material from attempted cyclisations of the diketone (16) .

On reduction, both or either of these acids would give the same product and the structure of the reduced acid (see p. 176) would then be (36), i.e. 4-phenylcycloheptane carboxylic acid. The fact that the reduction product had a sharp m.p. and appeared to be only one compound was rather surprising. Reduction of either of the acids, (29) or (35) would normally be expected to give rise to both <u>cis</u> and <u>trans</u> isomers. If the carboxyl group were strongly hydrogen bonded to the double bond, this would provide sufficient reason for a <u>cis</u> reduction to take place. There is, however, no evidence for hydrogen-bonding in the i.r. spectrum. It is possible that the acid molecule lies on the surface of the catalyst in such a manner as to make a <u>cis</u> reduction entirely possible. Were this so, the phenyl and the carboxyl groups of the reduced acid (36) would have a <u>cis</u> relationship to each other. An attempt was made to corroborate this fact by cyclisation of the reduced acid (36) to the tricyclic ketone (37). The reduced acid was heated with polyphosphoric acid. The product consisted entirely of neutral material (91%). The i.r. spectrum of the crude product showed strong carbonyl absorption at 1670 cm^{-1}. The normal absorptions in the regions 750, 690 cm^{-1} for a mono-substituted aromatic ring were absent, and were replaced by bands at 800, 775, 750 and 730 cm^{-1}, suggesting a mixture of 1:2-, 1:4-, and perhaps other substitution patterns. This suggested that a mixture of products was present, not surprisingly so since linear condensation products are known to occur in reactions with polyphosphoric acid[66]. The crude mixture was treated with an acidic solution of 2:4-dinitrophenylhydrazine and the precipitate chromatographed on 4:1 bentonite-kieselguhr. On elution with chloroform two fractions were obtained, the first a mixture which was discarded. The second fraction was further purified by sublimation and yielded an orange, high-melting derivative. Insufficient material was available for microanalysis, but mass-spectrometry showed a parent ion at 380 mass units ($C_{20}H_{20}N_4O_4^+$). This corresponds to the molecular weight expected for the 2:4-dinitrophenylhydrazone of the tricyclic ketone (37).

The Neutral Component.

The neutral fraction from attempted acid cyclisation of the diketone (16) (p. 175) was a solid which was recrystallised from light petroleum (b.p. 80-100°) as white needles, with a sharp m.p. (121°). T.l.c. of this material showed only one spot and the compound was thought to be 100% pure. It was later found (p. 200), however, to contain traces of the di-addition product (20) or (21) which had an identical R_f value and was not detected by t.l.c.. The material was therefore rigorously purified by treatment with sodium borohydride which reduced any extraceous ketonic material and left the required neutral compound unaffected. Chromatography on silica, followed by recrystallisation, gave a pure sample of the solid, m.p. 121°. Microanalysis showed the compound to have a possible molecular formula of $C_{14}H_{16}O_2$ i.e. isomeric with the acid (35) already discussed. The neutral compound was not oxidised by alkaline potassium permanganate, gave no precipitate with an acidic solution of 2:4-dinitrophenylhydrazine and was soluble in hot alkali. Acidification of the alkaline solution gave back the neutral material. The i.r. spectrum of the unknown compound indicated the presence of a γ-lactone. In carbon tetrachloride solution, carbonyl absorption was observed at 1780 cm^{-1} (ϵ, 90; $\Delta\nu_{\frac{1}{2}}$, 12.5 cm^{-1}). This was accompanied by a strong band at 1156 cm^{-1} (C - O str).

Experiments were carried out to show that the neutral compound was related to the acid previously described. The acid (35) was heated under reflux for 8 hours in a mixture of glacial acetic acid and aqueous sulphuric acid (50% by volume) and the product separated into acidic and neutral materials by extraction. The former was unchanged starting material while the latter, a yellow solid was shown to be the γ-lactone under discussion. Recrystallisation of the solid gave white needles, m.p. 115-120°; on admixture with a sample of the γ-lactone (m.p. 121°) the m.p. was not depressed. The i.r. spectra of the two materials were entirely superimposable and t.l.c. confirmed that they were identical.

Lactonisation of the acid (35) was also attempted using glacial acetic acid and concentrated hydrochloric acid, i.e. the conditions under which the acid and the γ-lactone were obtained from the diketone (16). The acid (35) was heated under reflux in glacial acetic acid and concentrated hydrochloric acid for 8 hours and the product separated into acidic and neutral materials. The acid fraction was unchanged starting material. The neutral fraction was shown by t.l.c. to be a mixture of three compounds. These were identified (t.l.c.) by comparison with known samples as the γ-lactone, the bicyclic ketone (13) and the diketone (16), the latter being present in very small amounts. On redissolving the crude product in ether, there remained a white solid residue which was recrystallised from light petroleum as needles, m.p. 117-120°. This material was identical with the γ-lactone with respect to their i.r. spectra with the exception of a slight shoulder on the carbonyl absorption band at 1745 cm^{-1}. Further recrystallisations did not remove this.

Bearing in mind the 1,4 relationship of the phenyl and carboxyl groups of the ring system involved, there were two γ-lactones possible, (38) and (39) each of which can have two epimeric forms. That the γ-lactone was (38) seemed unlikely; (39) appeared the more plausible structure on the evidence of the relationship between the acid (35) and the γ-lactone. A study of the n.m.r. spectrum, however, enabled a choice to be made between the alternative γ-lactones. The spectrum revealed the $-CO-C-\overset{|}{\underset{|}{C}}-H$ proton as a doublet (1,H) at 5.1τ ($J = 6.9$ cps) showing barely discernable sub-splitting. The lactone (38) demands a more intricate splitting and was rejected as a possible **structure.** It was seen from models that the <u>cis</u>-phenyl lactone (40) as represented in the most probable conformation (40a) would give rise to such a signal since the dihedral angles H_1H_2, H_1H_3 and H_1H_4 were close to 90°, 90° and 30° respectively. The observed coupling constant was also of the correct order[120]. The alternative epimeric structure (41) which also satisfied the n.m.r. spectrum was discounted on the grounds that this would require lactonisation to proceed via a <u>cis</u>-addition mechanism, whereas <u>trans</u>-addition to the double bond is usual in these reactions[121].

It was interesting to note that, were the structure of the lactone the one proposed, addition to the double bond must, in this instance, have taken place in an anti-Markownikoff manner. In general, the nucleophilic carboxyl group would attack the more stable carbonium ion, i.e. in this case, attack would take place preferentially at the tertiary carbonium ion (42) to give the δ-lactone (43), rather than at the secondary carbonium ion (44) which would yield the γ-lactone (40). This holds, however, only for reactions where steric factors are unimportant. It may be that, in the transition state, a greater overlap of the $2p$ orbitals of the carbonyl oxygen exists between the vacant orbital of the γ-carbonium ion than is possible with the δ-carbonium ion; since the two reactive centres must be sufficiently close to allow bond formation to occur. Further chemical evidence for the problem was therefore sought.

It was hoped that the δ-lactone (43) could be prepared for comparison with the unknown lactone. A study of its stability, and its possible rearrangement to the corresponding γ-lactone (40) would provide useful information. The proposed method of obtaining the δ-lactone (43) was via the corresponding bromo- or iodo- lactone. Bromo- and iodolactonisation experiments were therefore carried out on the acid (35) but neither met with any success. Treatment of the acid (35) with bromine in acetic acid resulted in a black oily mass which was then neutralised with sodium hydroxide. Ether and chloroform extracts from the reaction were examined. The former yielded a yellow oil shown by t.l.c. to contain four compounds. The chloroform extract afforded only a black tar. Both extracts were discarded. It was suspected that the intermediate dibromo compound was decomposing before lactonisation could occur in base, and a reverse procedure was therefore employed. In this case bromine was added slowly to a solution of the acid (35) in aqueous sodium hydroxide until excess of bromine was present. Chloroform and ether extracts of the reaction mixture were examined. The chloroform solution gave a low-melting solid which could not be recrystallised. T.l.c. showed it to be a mixture of four compounds. The mixture was not separated. The ether extract gave a yellow oil. T.l.c. showed only one spot with an R_f value equal to that of the γ-lactone. The i.r. spectrum, however, suggested the presence of a mixture since it showed hydroxyl absorption accompanied by three carbonyl absorptions. (1780, 1750 and 1730 cm^{-1}). Bromolactonisation was not further investigated.

Iodolactonisation of the acid (35) was attempted by the standard method but yielded no useful results. Both acidic and neutral materials were obtained. The acidic material was an iodine-containing solid which could not be purified.

The neutral material was chromatographed on silica and extensive decomposition occurred. No single pure compound could be isolated. Preparation of the δ-lactone (43) was therefore abandoned.

Since the structure proposed for the lactone was based principally on the evidence of the n.m.r. spectrum, confirmation of this structure by chemical means was sought. Hydrolysis of the γ-lactone (40) would give a hydroxy-acid which should be oxidisable by Jones's reagent to the corresponding keto-acid. The hydroxy-acid from the δ-lactone (43) would not be oxidisable in such a way, the hydroxyl function in this case being a tertiary one. Hydrolysis and oxidation to the corresponding keto-acids would not distinguish between the epimeric lactones (40) and (41), but the carbonyl and carboxyl groups were considered potentially useful for further distinguishing reactions.

The lactone was first refluxed in 10% aqueous sodium hydroxide containing sufficient ethanol to effect solution. The product consisted largely of unchanged lactone but a very small amount of an acidic material was obtained. This was not purified but was oxidised in the crude state with Jones's reagent. The yield of material was small enough to preclude any further investigation although 2:4-dinitrophenylhydrazone formation indicated the presence of a carbonyl function. Attempted hydrolysis of the lactone with

35% sodium hydroxide gave, similarly, unchanged starting material and an ether-insoluble precipitate. The latter material was water-soluble, its i.r. spectrum showed strong hydroxyl absorption at 3400 cm^{-1} and two bands (1550, 1420 cm^{-1}) such as might be given by a carboxylate anion. Use of an acidic oxidising agent was avoided by treating this material with a solution of chromium trioxide in pyridine. The product, a white crystalline solid was identified as the starting lactone.

The indication in the above experiment being that it was possible to form the sodium salt of the hydroxy-acid produced, it was hoped that treatment of the salt with methyl iodide would yield the corresponding methyl ether and re-lactonisation would thus be prevented. The dry sodium salt was suspended in acetone and refluxed with excess of methyl iodide. The product, a yellow solid, had an anomalous m.p. (75-80°, with crystals appearing at 140°, to remelt at 240°). T.l.c., however, showed only one spot, corresponding to the known lactone. Recrystallisation of the crude material yielded lactone only.

An alternative procedure designed to open the lactone was reduction with lithium aluminium hydride. At the first attempt the lactone was refluxed for 5 hours with a suspension of lithium aluminium hydride in dry tetrahydrofuran. The product was a yellow sticky oil which solidified on cooling. Recrystallisation of the solid proved exceedingly difficult and generally resulted in oils or soft solids. A sample, recrystallised several times from water, was eventually obtained as white needles, m.p. 80-85°. T.l.c., however, showed that even this sample was impure and contained three compounds, one of which was the starting lactone, present in very small amounts. Chromatography of the strongly adsorbed material was impossible, but it was found that a longer reflux time (7.5 hours) removed all traces of the starting lactone. The product was then a crystalline solid contaminated by traces of another strongly adsorbed material. It was shown by its i.r. spectrum to be an alcohol, with strong absorption at 3363 cm^{-1} and at 1073, 1020, and 993 cm^{-1}. Purification was therefore attempted by acetylation and benzoylation of the product but in neither case was this successful. The product from acetylation was an oil shown by t.l.c. to be a mixture of two compounds. The i.r. spectrum of the immediate product showed absence of hydroxyl absorption, a broad carbonyl band at 1738 cm^{-1} and strong absorption at 1248 cm^{-1}. Attempted crystallisation and prolonged standing of the material gave rise to the presence of a hydroxyl function. The product from benzoylation appeared to be a mixture of mono- and dibenzoates. It was impossible to work with the material without considerable hydrolysis taking place. Purification via esterification was thus useless.

All work on the product from hydride reduction had to be carried out on a material which although crystalline, was known to contain traces of an impurity. Analysis of the material was sufficiently accurate to indicate that it did have a molecular formula of $C_{14}H_{20}O_2$, as expected. The n.m.r. spectrum, in deuterochloroform showed a poorly resolved multiplet (1,H) centred at 5.98τ (assigned to proton of a secondary alcohol C$\underline{H}$OH) and a doublet (2,H) at 6.54τ (J = 5 cps) assigned to the methylene protons of a primary alcohol (-O-$\underline{CH}_2$ - $\overset{|}{\underset{|}{\mathrm{C}}}$H). When the spectrum was recorded in dimethylsulphoxide[122] the secondary and primary hydroxyl protons were observed respectively as a doublet at 5.78τ (J = 4.8 cps) and a triplet at 5.5τ (J = 4.8 cps), each corresponding to one proton. The structure of the diol is most probably as shown (45).

Jones's oxidation of the diol was carried out at 0° with a calculated amount of reagent and at 15° with excess of reagent. The result was the same in both cases. The product was a semi-solid shown by t.l.c. to be a mixture of four compounds. One of these was separated out by trituration of the crude material with ether. It was identified as the di-addition product (20) or (21) and presumably had been present in the starting lactone. On reduction it would give a triol, almost certainly the contaminating material present in the diol (45); the triol, on oxidation would once more give the trione (20) or (21) . The lactone used for the hydride reduction was a recrystallised sample and showed only one spot by t.l.c. Only one carbonyl band was observed in the i.r. spectrum. It was at this point that it was realised that the R_f values of the lactone and the di-addition product were identical and that further purification of the lactone was essential (see p. 192).

Removal of the trione (20) or (21) from the oxidation product left a viscous yellow oil which was found to be a mixture of several compounds. The i.r. spectrum showed acidic hydroxyl absorption and a broad unresolved carbonyl band (ca. 1740-1680 cm^{-1}). The mixture was not separated and it may be concluded that oxidation of the diol (45) did not proceed in a simple manner.

It is now possible to have an overall picture of the reactions taking place when the diketone (16) is treated with acetic acid and hydrochloric acid (or indeed, under a variety of acidic conditions). Firstly, it becomes clear why the ratio of acidic: neutral material from the attempted cyclisation reaction varies with time (p. 175). Longer reaction times will promote the formation of correspondingly greater amounts of γ-lactone (i.e. neutral fraction) at the expense of the acidic material.

In the attempted lactonisation of the acid (35) the product was found to contain not only the lactone (40) but also the bicyclic ketone (13) and the diketone (16). These findings suggest that not only is the γ-lactone (40) obtainable from the acid (35) but that an equilibrium is set up between the acid and the bicyclic ketone (13) to which it may revert under acid conditions. The bicyclic ketone, in turn, must be reversibly in equilibrium with the diketone (16) since it was found to be present. (Scheme B_1). Included in this scheme must be the reversible equilibrium pertaining to the two isomeric acids (29) and (35). The mechanism proposed for the opening of the bicyclic ketone (13), shown to be a precursor of the acid (35), requires the initial production of the acid (29). Both the acids (29) and (35) are capable of lactonisation but only (35) can give a γ-lactone. It is generally held that γ-lactones are more stable than δ-lactones and it may be assumed that the γ-lactone (40) is formed preferentially, thus upsetting the equilibrium between the two acids and driving the reaction to the right (Scheme B_2). The acid (35) and its γ-lactone will themselves, however, be thermally in equilibrium. (The lactone oxygen atom is β to a phenyl ring and the acid (35) would be obtained by β-elimination). The whole system which is in equilibrium under acid conditions may then be written as shown (Scheme B_3). Factors which will determine the exact position of equilibrium will be the stability of the bicyclic ketone (13) (whose high carbonyl absorption in the i.r. indicates ring strain) and the ease of formation of the γ-lactone (40).

The crude acidic material from treatment of the diketone (16) with glacial acetic acid and hydrochloric acid was examined more closely to see if the presence of the two isomers (29) and (35) could be detected. T.l.c. examination consistently showed apparently one compound. At this time, other work[123] being carried out in this department on related compounds suggested that g.l.c. examination of the ester might prove more informative. Esterified material had, like the acidic material, shown only one compound on t.l.c. examination, but g.l.c. did in fact indicate the presence of two isomers. These could not be separated either by chromatography or by distillation. It may be concluded from this that both acids were indeed present. The mixture of products obtained from ozonolysis (see p.179) of the acidic material may be explained on the basis of there being two acids present. The particular keto-diacid isolated, (34) would appear to be present in larger amounts and was therefore obtained preferentially. An additional factor in the preferential isolation of the keto-diacid (34) may be the relative solubilities of the products the diacid obtained in essence, a substituted succinic acid while the keto-diacid (31) which would be obtained on cleavage of the acid (29) is a substituted glutaric acid. Succinic acid itself is approximately ten times less soluble (in water) than glutaric acid, and if the same relationship held only approximately for the substituted acids, the keto-diacid (34) is the one more likely to be isolated.

Obviously there still remains a considerable quantity of work which could be done to establish conclusively the presence of both the acids (29) and (35) and to investigate the equilibrium between them. It might well be that examination of the residues from ozonolysis would furnish the other keto-diacid (31). Lack of time, however, precluded any further work on this topic for the present.

The results obtained from attempted cyclisation of the diketone (16) and from work on the bicyclic ketone (13) prompted an inquiry into why ring-opening should be observed in the ketone (13) but apparently not in the cases of the analogous bicyclic ketones (12) and (14), both of which were readily obtained (see p.171). The answer appeared to be simply that considerable ring strain would be present in the bicyclic ketone (13) which contained two five-membered rings, and whose size occasioned considerable interaction between the carbonyl group and the double bond. There is indeed evidence for ring strain in similar bicyclic systems. 2-Methyl-5-carbethoxybicyclo-[3:2:1]-oct-2-en-8-one (46)[124] shows cyclopentanone carbonyl absorption at 1760 cm^{-1} in the infra-red, while the absorption of the cyclopentanone carbonyl of bicyclo-[3:2-1]-2:8- dione (47)[125] is observed at 1754 cm^{-1}. Carbonyl absorption in the bicyclic ketone (13) under discussion occurs at 1758 cm^{-1}. This strain would be considerably less in the bicyclic ketones (12) and (14).

Accordingly, the acid cyclisation of the diketones (15) and (17) and the stability of the respective products (12) and (14) was re-investigated.

The product from acid cyclisation of the diketone (15) was examined for the presence of any acidic material, but none was found. The bicyclic ketone itself (12) was treated with a number of acids and in every case, except one, was recovered intact. The ketone (12) proved stable to treatment with concentrated sulphuric acid, and concentrated hydrochloric acid. On treatment with a mixture of perchloric acid and acetic acid the product, as before, was largely unchanged ketone (12). This was accompanied, however, by a minute amount of an acidic material. The yield of this was so small that no data for it could be recorded.

A re-investigation into the products from acid cyclisation of the diketone (17) revealed that acidic material was actually present, but only to the extent of 0.5% of the total product (i.e. a yield of 0.35% from the diketone). An increased reaction time (75 hours) did show a corresponding increase in acidic material. A ratio of acidic:neutral material of 10%:90% was then obtained, raising the overall yield of acidic material to 8.2%. The acid was not obtained in sufficient quantity to be identified but an attempt was made to convert it into the corresponding γ-lactone by treatment with glacial acetic acid and concentrated sulphuric acid. This however yielded a mixture of five compounds, two of which were shown (t.l.c.) to be the diketone (17) and bicyclic ketone (14) respectively. This suggests that the same type of equilibrium exists here as was observed in the case of 2-phenylbicyclo-[3:2-1]-oct-2-en-8-one (13) (p. 202 . and Scheme B_3) but the position of equilibrium is obviously different.

Compared to the bicyclic ketone (13), its analogues (12) and (14) demonstrated remarkable stability in acid conditions.

The reaction described (p. 175) provided easy access to a seven-membered ring and appeared potentially useful for the synthesis of compounds.containing such a ring system (e.g. colchicine (48)) and substituted azulenes. Its possible application was tested by carrying out the same reaction on the 1:5-diketone, β-(2-oxocyclopentylmethyl)-α-hydrindone (54).

α-hydrindone (51) was initially prepared by decarboxylation of 1-keto-3-carboxyindane (50), but more satisfactorily by polyphosphoric acid cyclisation of β-phenylpropionic acid (49). A neutral by-product obtained in the latter reaction was a yellow-green crystalline solid (m.p. 144-146°) which turned brown on standing for some time. It was shown by t.l.c. to be a pure compound. Microanalysis gave a possible molecular formula of $C_{18}H_{14}O$ and mass-spectrometry confirmed this, a parent ion being obtained at 246 mass units ($C_{18}H_{14}O^{+}$). The i.r. spectrum showed a single carbonyl band at 1670 cm^{-1} (α-hydrindone itself absorbs at 1700 cm^{-1}) accompanied by an intense band at 1610 cm^{-1}. A single band at 750 cm^{-1} indicated <u>ortho</u> substitution of a benzene ring. The compound gave an unstable 2:4-dinitrophenylhydrazone. On the above evidence, the structure of the by-product was postulated as 2-(hydrindylidene-1)-α-hydrindone (52) from condensation of two molecules of α-hydrindone (51). Self-condensation seemed more likely to give the isomeric 3-(hydrindylidene-1)-α-hydrindone (53). Literature reports of the preparation of α-hydrindone (51) are many and the only by-product which seems to have been observed is (53) but in every case this is reported as a high-boiling oil, which the by-product in our case was not. The position of the carbonyl band in the i.r. spectrum of the solid by-product also lends weight to the argument that an $\alpha\beta$-$\alpha'\beta'$-unsaturated ketone is present. Although cyclisation of the acid (49) to α-hydrindone (51) under various conditions has been reported[126], no mention is made of polyphosphoric acid so that no comparison of other workers' results with our own could be made. Kipping[127] did however, in 1894, isolate a yellow crystalline solid, m.p. 142-143°, from treatment of α-hydrindone with dilute sulphuric acid which he postulated as 2-(hydrindylidene-1)-α-hydrindone (52).

The Mannich base hydrochloride of α-hydrindone was prepared in the usual way but liberation of the free base proved unsatisfactory. A low yield (10%) of an impure product was obtained on liberation with sodium hydroxide. Liberation of the free base with 5% ammonium hydroxide gave a cleaner product, in 35% yield.

The diketone (54) was prepared as before (p. 170). Two products were obtained and the required compound (54) isolated by fractional crystallisation. The other product, which was not investigated was probably a di-addition compound, by analogy with previous cases. The diketone (54) was heated under reflux for 8 hours in a mixture of glacial acetic acid and hydrochloric acid and yielded both acidic and neutral material (78%:22%). The acidic material was a white crystalline solid with two m.p.'s (at 158-160° and again at 168-169°). It is possible that lactonisation of the acid occurred at the m.p., since t.l.c. of the material showed only one spot. Microanalysis gave the expected molecular formula, $C_{15}H_{16}O_2$. The n.m.r. spectrum showed complete absence of vinyl protons.

From these results it was concluded that the acid obtained in this case was the isomer (55). The fact that only one acid was obtained in this case was not unexpected, since the isomer (55)has a double bond in the tetra-substituted state, achievement of which would provide a driving force for the isomerisation (56)$\longrightarrow$(55).

The neutral fraction from the reaction was a mixture of three compounds, one of which was identified (t.l.c.) as the diketone (54). The R_f values of these materials were very similar and chromatographic separation was not possible. The expected lactone (57) was not isolated. An attempt was made to obtain it by lactonisation of the acid (55) which was refluxed in glacial acetic acid and concentrated hydrochloric acid for 24 hours. The yield of neutral material (0.6 mg.) was only 0.0001% and prohibited any further investigation. T.l.c. however showed that the neutral material was a single compound with an R_f value different from that of the diketone (54).

As previously, it was found possible to prepare the bicyclic ketone (58) by cyclisation of the diketone (54) in dry benzene, using p-toluenesulphonic acid as catalyst, and removing any water formed. The bicyclic ketone (56) was obtained in 72.4% yield as a white crystalline solid. The i.r. spectrum (nujol) showed a single carbonyl absorption at 1745 cm^{-1}. The n.m.r. spectrum showed complete absence of vinyl protons as expected.

On the evidence so far obtained, it would appear that the stability (or otherwise) of the bicyclic systems examined (12), (13), (14), (56) depended on the ring size of the system and the concomitant ring strain. Enormous scope obviously exists for further investigation in this field. The reactions carried out so far have, of necessity, been limited to a few but further work on that reaction involving a bicyclo-[3:2:1]-ketone intermediate should prove both interesting and useful as a synthetic method to seven-membered rings. The advantages of being able to synthesise a seven-membered ring system with substituents in any required position would be considerable. As has been shown, the reaction also applies to fused ring systems. Opportunity therefore exists for examining the same reaction on a series of diketones of different types.

EXPERIMENTAL - PART II.

Preparation and reactions of 2-phenylbicyclo-[3:3:1]-non-2-en-9-one (12).

β,β'-dimethylaminopropiophenone hydrochloride.

The Mannich base was prepared as its hydrochloride by the method given in "Organic Synthesis"[128]. It was obtained in 92% yield as a solid, m.p. 140-144°. The product was recrystallised from a mixture of 95% ethanol and acetone. The large white hexagonal crystals (m.p. 142-144°) were hygroscopic; on further drying they had m.p. 152-153°.

2-(β-Benzoylethyl)-cyclohexanone (15).

(a) The diketone (15) was prepared by the method of Cope and Hermann[113]. Technical cyclohexanone was redistilled from calcium chloride. The reaction product, a red oil, was distilled, b.p. 152-170°/0.5 mm., with a small fore-run whose i.r. spectrum showed no aromatic absorptions but which was not identical to that of cyclohexanone. The bulk of the product, on cooling, slowly solidified. The required diketone (15) was crystallised from cyclohexane - light petroleum mixtures as white needles, m.p. 49-50°; ν_{CO} 1700 cm^{-1} (ring ketone) and 1680 cm^{-1} (aryl ketone).

(b) The diketone (15) was prepared by a modification of the method used by Gill *et al*.[114] for the analogous diketone (16).

ββ'-Dimethylaminopropiophenone was liberated from its hydrochloride by suspension in water, addition of aqueous sodium hydroxide and extraction of the precipitated free base. Freshly prepared Mannich base and redistilled cyclohexanone in a molar ratio of 1:3 were heated together at 160° for 20 minutes; evolution of dimethylamine was observed. The cooled reaction mixture was exactly neutralised with glacial acetic acid and extracted into ether. The ethereal extract was washed with brine, dried and concentrated. Excess of cyclohexanone was removed on a water-pump and the residue distilled under reduced pressure to give a pale yellow oil which solidified on cooling. The diketone (15) crystallised from light petroleum as white needles, m.p. 48-50°, identical with the product obtained in (a). From 50g. of the Mannich base, the yield of diketone (15) was 36.6 g. (80%).

2-Phenylbicyclo-[3:3:1]-non-2-en-9-one (12).

The method of Cope and Hermann[113] was used. A solution of the diketone (15) in glacial acetic acid (250 ml.) and concentrated hydrochloric acid (50 ml.), on heating under reflux for 16 hours afforded the required ketone (12) as a yellow oil, b.p. 130-133°/0.15 mm. (22g.; 74%) which solidified on trituration with light petroleum. The solid was recrystallised from cyclohexane-light petroleum as fine white needles, m.p. 52-53°. The i.r. spectrum (carbon tetrachloride) showed ν_{CO} at 1732 cm^{-1} (ϵ, 444) and 1722 cm^{-1} (ϵ, 313); in chloroform, carbonyl absorption occurred at 1729 cm^{-1} (ϵ, 291) and 1715 cm^{-1} (ϵ, 437), and in hexane at 1736 cm^{-1} (ϵ, 504) and 1724 cm^{-1} (sh, ϵ 160). The compound became oily on standing and developed hydroxyl functions (as seen from i.r. spectra), but was restored to its original form on distillation. The n.m.r. spectrum (carbon tetrachloride) was poorly resolved and may be attributed to partial decomposition. Signals were observed at 2.8τ (multiplet, aromatics), 3.8τ (triplet, J = 4 cps, olefinic proton), 6.5τ (unresolved band, probably proton on C_1), 6.7τ (unresolved), 7.1-8.5τ (broad unresolved band).

Reactions of 2-phenylbicyclo-[3:3:1]-non-2-en-9-one (12).

(a) Perbenzoic acid:- A solution of the ketone (12) (2g.) in chloroform was treated with a solution of perbenzoic acid in chloroform and allowed to stand at 0° for 72 hours. The ketone (12) was recovered unchanged.

(b) Peracetic acid-sodium acetate[129]:- The ketone (12) (4g.) in glacial acetic acid (4 ml.) was treated with 40% peracetic acid (20g.) containing sodium acetate (4g.) and left at room temperature for 92 hours. The solution was diluted with water and neutralised with aqueous sodium hydroxide. Extraction yielded a solid product which was identified (i.r., m.p.) as the starting ketone (12).

(c) Trifluoroperacetic acid[130]:- To a mixture of 80-90%

hydrogen peroxide (1 ml.) and methylene chloride (5 ml.) at 0° was added trifluoroperacetic acid (4 ml.). The mixture was allowed to stand for a short time in ice, then added portion-wise to a solution of the ketone (12) (4.2g.) in methylene chloride (20 ml.) containing disodium hydrogen phosphate (12g.). When the vigourous reaction subsided, the mixture was warmed (steam-bath) for 30 minutes, cooled and poured into water. Extraction with methylene chloride gave a straw-coloured oil which turned to an intractable glass on cooling.

(d) Sulphuric acid:- The ketone (12) (2g.) was added to concentrated sulphuric acid (8 ml.) at 0°, to give a red solution. The reaction mixture was allowed to stand at room temperature for 19 hours, with occasional shaking, then poured onto ice. Extraction with ether gave a yellow oil which solidified on cooling, identified (i.r.) as unchanged starting material.

(e) Hydrochloric acid:- The ketone (12) (2g.) was treated with concentrated hydrochloric acid (8 ml.) but did not dissolve. The mixture was warmed, treated with a further portion of acid (10 ml.) and warmed again. The ketone (12) still did not dissolve and the reaction was abandoned.

(f) Perchloric acid/acetic acid:- The ketone (12) (2.4g.) was dissolved in 72% perchloric acid (8 ml.) and acetic acid (2 ml.) and the cherry-red solution left overnight at room temperature. The reaction mixture was poured onto ice, the solid product filtered, taken up in ether and the ethereal solution washed with aqueous sodium hydroxide, with brine and dried. The neutral ethereal extract afforded an oily product, identified (i.r.) as the starting ketone (12). Acidification and extraction of the basic solution gave a negligible amount of a brown oil with a butyric acid-like odour.

Preparation and reactions of 7-phenylbicyclo-[4:3:1]-dec-7-en-10-one (14).

2-(β-Benzoylethyl)-cycloheptanone (17).

The diketone (17) was prepared exactly as for the diketone (15) [Method (b)]. 69g. of the Mannich base yielded 58g. (61%) of a brown oil which distilled to a yellow oil, b.p. 162-167° (0.35 mm.). T.l.c. showed the oil to be a mixture of two compounds with very similar R_f values. On cooling and scratching the material was induced to solidify. The required diketone (17) was isolated from the mixture by recrystallisation from light petroleum. This procedure occasioned considerable loss but gave the diketone (17) (35g.; 36%) as a pure compound (t.l.c.), white needles, m.p. 27° (Found: C, 78.41; H, 7.87. $C_{16}H_{20}O_2$ requires C, 78.65; H, 8.25%). The i.r. spectrum showed ν_{CO} 1702 cm^{-1} (ring ketone) and 1693 cm^{-1} (aryl ketone).

7-Phenylbicyclo-[4:3:1]-dec-7-en-10-one (14).

(a) Glacial acetic acid/hydrochloric acid, 8 hours:- A solution of the diketone (17) (3g.) in glacial acetic acid (25 ml.) and concentrated hydrochloric acid (6 ml.) was heated under reflux for 8 hours, excess of acetic acid removed under reduced pressure and the residue flooded with water. The mixture was extracted into ether and the ethereal extract washed with aqueous sodium hydroxide, with brine, and dried. The basic solution on acidification and extraction gave a brown oil (0.0104g.; 0.35%) whose i.r. spectrum showed carboxylic acid absorptions (ν_{OH} 3500-2900 cm^{-1}, ν_{CO} 1710 cm^{-1}). The neutral ethereal extract gave a yellow viscous oil (2.2 g.; 79.1%) which partially solidified on standing. The i.r. spectrum showed carbonyl absorption (ca. 1700 cm^{-1}) and the typical fine structure of a bicyclic system (780-740 cm^{-1}). T.l.c. showed that five compounds were present, one of which was identified (R_f value) as the starting diketone (17) and another as the required bicyclic ketone (14), by comparison with the product from (b), below. The ratio of acidic:neutral material was 0.5%:99.5%.

75 hours:- the reaction was repeated with a reflux time of 75 hours. The yield of acid was 8.2%; the neutral material again contained five compounds. The ratio of acidic:neutral material was 10%:90%.

Attempted lactonisation of the acidic material.

The acidic material (0.5g.) from the above reaction was heated under reflux for 15 hours in a solution of glacial acetic acid (10 ml.) and concentrated sulphuric acid (1 ml.). Excess of acetic acid was removed under reduced pressure, the residue diluted with water and extracted with ether. The ethereal extract was washed with brine, with aqueous sodium carbonate, with brine again and dried. The basic extract contained a negligible amount of the starting acid. Concentration of the neutral ethereal solution gave a semi-solid; shown by t.l.c. to contain five compounds. Two of these were identified (R_f values) as the diketone (17) and the bicyclic ketone (14) respectively. The mixture was not separated.

(b) p-Toluenesulphonic acid:- p-toluenesulphonic acid (3g.) was heated under reflux in dry benzene (125 ml.) removing any water present by means of a Dean and Stark water separator[119]. Once all the acid had dissolved (40 minutes) the diketone (17) (3g.) was added and the mixture heated under reflux for 2.5 hours, removing any water formed. Solid potassium carbonate was added to the hot solution and the mixture allowed to cool. The reaction mixture was filtered and the filtrate evaporated to give a brown mobile oil (2.2g.; 79.2%), shown to consist of a mixture of four compounds. Chromatography of the product on silica (40g.) gave the required ketone (14) as an oil which was induced to crystallise by trituration with light petroleum. The material was recrystallised with difficulty from hexane-light petroleum (b.p. 40-60°) as a white solid, m.p. 40°. The m.p. of the solid, kept at 0° in the dry state, rose to 78-80°. A sample of the latter material, on recrystallisation from light petroleum (b.p. 40-60°) by slow evaporation of the solvent gave a white solid, m.p. 40°. The i.r. spectra of the two materials of different m.p. were identical. T.l.c. showed the material to be a pure compound (Found: C, 85.15; H, 7.76. $C_{16}H_{18}O$ requires C, 84.93; H, 7.99%). The i.r. spectrum (carbon tetrachloride) showed ν_{CO} 1718 cm^{-1} (ϵ 474) and 1710 cm^{-1} (sh, ϵ 248). In chloroform, carbonyl absorptions were observed at 1715 cm^{-1} (sh, ϵ 222) and 1705 cm^{-1} (sh, ϵ 350) while in hexane carbonyl absorptions occurred at 1725 cm^{-1} (ϵ 252) and 1710 cm^{-1} (sh, ϵ 95).

The n.m.r. spectrum (deuterochloroform) showed signals at 2.66τ (multiplet, 5H; aromatic protons), 3.98τ (poorly resolved triplet, 1H; olefinic proton), 6.45τ (unresolved band, 1H; proton on C_6), 7.1-7.9τ (unresolved band, 3H; proton on C_1 and allylic protons on C_9) and 8.2-8.88τ (multiplet, 8H; methylene protons.

The ketone (14) gave a yellow 2:4-dinitrophenylhydrazone, recrystallised from ethanol as needles and plates, m.p.

218-220° and from dioxan-ethanol mixtures as needles, m.p. 223°. The derivative was unstable to heat, in solution.

Preparation and reactions of 2-phenylbicyclo-[3:2:1]-oct-2-en-8-one (13).

2-β-(Benzoylethyl)-cyclopentanone (16).

(a). The diketone (16) was prepared in the same way as the diketone (15)[Method (a)]. Cyclopentanone (112g.) and sodium hydroxide (111 ml., 6N) were added to ββ'-dimethylaminopropiophenone hydrochloride (66g.) in ethanol (500 ml.) at boiling point, and heated under reflux for 15 minutes. Acidification and extraction gave an oil which was fractionated to give

1. a colourless oil, b.p. 70-100°/0.1 mm., whose i.r. spectrum showed no aromatic absorptions and did not correspond to that of cyclopentanone.

2. a yellow oil, b.p. 150-170°/0.1 mm., which solidified on cooling and scratching. Recrystallisation from cyclohexane-light petroleum gave the required diketone (16) (37g.) as off-white needles, m.p. 40-42°, ν_{CO} 1737 cm^{-1} (ring ketone) and 1686 cm^{-1} (aryl ketone).

(b) The diketone (16)[114] was prepared in the same way as the diketone (15) Method (b) . Distillation of the crude product gave an oil which solidified on cooling. The required diketone

(16) was recrystallised from light petroleum as white needles, m.p. 40-42°, identical with the product obtained in (a) above. The yield of diketone was 73%. The residue from the distillation was extracted with benzene and on addition of light petroleum, a solid was precipitated. The solid was recrystallised several times from light petroleum and finally from ether as fine white needles, m.p. 115°. (Found: C, 79.62; H, 6.84. $C_{23}H_{24}O_3$ requires C, 79.28; H, 6.94%). The i.r. spectrum showed ν_{CO} 1735 cm^{-1} (cyclopentanone) and 1692 cm^{-1} (aryl ketone) The n.m.r. spectrum (deuterochloroform) showed the following signals:- multiplet at 2.0τ (4H, assigned to aromatic protons adjacent to a carbonyl function), multiplet at 2.4τ (6H, remaining aromatic protons), triplet at 6.85τ (J = 7 cps; 4H, assigned to $-CH_2CO-Ph$ protons), unresolved multiplet centred on 7.85τ, and multiplet at 8.3τ (10H in total).

<u>Attempted preparations of 2-phenylbicyclo-[3:2:1]-oct-2-en-8-one (13)</u>. see Table II.

(a). <u>Acetic acid/hydrochloric acid, 48 hours</u>:- a solution of the the diketone (16) (37g.) in glacial acetic acid (300 ml.) and concentrated hydrochloric acid (75 ml.) was heated under reflux for 48 hours. Excess of acetic acid was removed under reduced pressure, the residue diluted with water, and extracted with ether. The ether extract was washed with brine, aqueous sodium hydroxide, more brine and dried. Concentration of the ethereal layer gave a neutral material (18.16g.) (the lactone (40); for properties and reactions see p. 239). Acidification and extraction of the sodium hydroxide extract gave a viscous brown oil (7.83g.) (the acids (29),(35); for properties and reactions see p. 226). The ratio of neutral:acidic material was 70%:30%.

(b). Acetic acid/hydrochloric acid, 8 hours:- experiment (a) above was repeated with a reflux time of 8 hours. The total yield of product was 32.1g. (87%) consisting of the lactone (40) (4.45g.) and acidic material [(29), 35)] (27.65g.) in a ratio of 14%:86%.

(c) Acetic acid/hydrochloric acid/sodium sulphite:- a solution of the diketone (16) (10.8g.; 0.05 mole) and sodium sulphite heptahydrate (13g.; 0.05 mole) in glacial acetic acid (100 ml.) and concentrated hydrochloric acid (25 ml.) was heated under reflux for 8 hours. The reaction mixture was worked up as in (a) and gave both neutral and acidic materials. The neutral material was identified (t.l.c.) as a mixture of the lactone (40) and the starting diketone (16), the acidic material as the acids (29), (35).

(d) Concentrated sulphuric acid:- treatment of the diketone (16) (5g.) with concentrated sulphuric acid (50 ml.) at room temperature gave only unchanged diketone (16). No acidic material was isolated.

(e) Hydrochloric acid/dioxan:- a solution of the diketone (16) (4g.) in dioxan (40 ml.) and hydrochloric acid (4 ml., 6N) was warmed (steam-bath) for 3 hours. The process afforded only unchanged diketone (16).

(f) Perchloric acid/dioxan:- a cooled solution of the diketone (16) (1g.) in dry dioxan (20 ml.) was added dropwise to a mixture of perchloric acid (6 ml.) and dry dioxan (300 ml.) at 0°. The mixture was allowed to stand at room temperature for 48 hours, then divided into two portions.

1. The solution was poured into water and extracted with ether. The washed and dried ethereal solution, on concentration, aff afforded an oil which solidified on cooling. It was identified (i.r., m.p.) as the diketone (16).

2. The solution was warmed (steam-bath) for 2 hours, gradually darkening in colour, and was worked up as in 1, to yield an orange oil whose i.r. spectrum showed hydroxyl absorptions of the acidic type. The oil was therefore dissolved in ether and separated into acidic and neutral fractions. The acidic fraction was a brown oil, identified (i.r.) as the acids (29), (35). The neutral fraction was unchanged diketone (16).

(g). Sodium methoxide/methanol:- a solution of the diketone (16))(129 mg.) in methanol (25 ml.) containing sodium methoxide (45.2 mg.) was allowed to stand at 20° for 24 hours with occasional shaking. The solution was acidified (acetic acid) to pH6, diluted with water and excess of methanol removed under reduced pressure. The residue was extracted with ether. The ethereal solution was washed with brine, with saturated sodium hydrogen carbonate, dried and concentrated to give a solid, identified as the diketone (16). Acidification of the basic extract afforded no acidic product.

Repetition of the above with an additional reflux time of 2 hours afforded unchanged diketone (16) and a minute amount of an unidentified acidic material.

(h) Hydrogen chloride (g)/ethanol:- a solution of the diketone (16) (10.8g.) in anhydrous ethanol (50 ml.) was saturated with gaseous hydrogen chloride. The reaction mixture was heated under reflux for 2 hours, excess of ethanol removed, the residue poured into water and the whole extracted with ether. Separation into acidic and neutral components was effected in the usual way. The acidic fraction was a negligible amount of a brown oil, identified as the acidic material [(29), (35)], previously obtained. The neutral fraction, a yellow oil (7g.; 70.3%) was shown by t.l.c. to be a mixture of three compounds. Chromatography of the neutral material on alumina (grade I; 150g.) gave the following materials:-

1. a **mobile** yellow oil, eluted with 5% ethyl acetate-light petroleum. The oil had an ester-like odour and its i.r. spectrum showed ν_{CO} 1740 cm^{-1} and ν_{C-O} 1250-1150 cm^{-1}.

Hydrolysis of a sample of the material (117 mg.) with methanolic potassium hydroxide gave a viscous yellow oil (63 mg.) identical with the acidic material [(29), (35)] previously obtained.

2. a yellowish solid, eluted with 10% ethyl acetate-light petroleum. Recrystallisation from light petroleum gave an impure material, white needles, m.p. 99-104°, ν_{CO} 1730 and 1680 cm^{-1}. The material was identified however (i.r., t.l.c.) as the di-addition product [(20) or (21)].

3. a yellow oil, eluted with 20% ethyl acetate-light petroleum whose i.r. spectrum showed it to be a mixture of the di-addition product [(20) or (21)] and an unidentified hydroxyl-containing compound (ν_{OH} 3500 cm^{-1}), which also showed carbonyl absorption (ν_{CO} 1760 cm^{-1}).

(i) Hydrogen chloride (g)/carbon tetrachloride:- the reaction was carried out as in (h), using 2g. of diketone (16) with a reflux time of 3 hours. No acidic material was present in the product which consisted solely of unchanged diketone (16).

(j) Hydrogen chloride (g)/dry *t*-butanol:- the procedure was as in (h) and afforded only unchanged diketone (16).

(k) Hydrogen chloride (g)/dioxan:- the reaction was carried out as in (h), using 5g. of diketone (16) and a reflux time of 1 hour only. The neutral fraction of the product was unchanged diketone (16) while the acidic fraction was a minute amount of the acidic material [(29), (35)] previously obtained.

(1) Boron trifluoride etherate/dry benzene:-

At 20°:- a solution of the diketone (16) (450 mg.) in dry benzene (10 ml.) was treated with a solution of boron trifluoride etherate (2 drops) in dry benzene (10 ml.), keeping the temperature below 5°. The solution was allowed to stand at 20° for 1 hour, then diluted with ether (40 ml.), washed rapdily with 5% sodium acetate solution (1 x 10 ml.), brine and dried. Concentration of the et ereal solution gave unchanged diketone (16).

Repetition of the experiment with a reaction time of 24 hours again gave the diketone (16) only.

At reflux temperature:- a solution of boron trifluoride etherate (12 ml.) in dry benzene (40 ml.) was added over 30 minutes to a solution of the diketone (16) (20g.) in dry benzene (400 ml.) and the solution heated under reflux for 3 hours. The dark red solution was cooled, diluted with ether, washed with 5% sodium acetate solution (2 x 250 ml.), with aqueous sodium carbonate, and dried. Acidification and extraction of the basic solution gave the acidic material [(29), (35)] previously obtained (5.04g.). Concentration of the neutral ether extract gave a semi-solid (11.23g.; 61%) shown by t.l.c. to be a mixture of two compounds. Chromatography on alumina (grade I, neutral; 200 g.) caused severe decomposition and several materials (both neutral and acidic) were eluted. These included

1. A colourless oil (3.03g.; 27% of total recovered material), eluted with 1-5% ether-light petroleum. The oil solidified on standing, m.p. 40-41°, ν_{CO} 1760 cm^{-1}. On admixture with a sample of the diketone (16) (m.p. 40-42°), the m.p. was depressed. Attempted recrystallisations of the material resulted in oils but it was shown by comparison (t.l.c., i.r.) with a pure sample obtained later (p. 245) to be the required bicyclic ketone (13).
2. A white crystalline solid (1.86g.; 16% of total recovered material) eluted with 20-65% ether-light petroleum, recrystallised from light petroleum as white needles, m.p. 110-112°. The solid was identical (i.r., mixed m.p.) with the di-addition product [(20) or (21)].
3. A brown oil (5.5g.; 49.4% of total recovered material), eluted with methanol, identified (i.r., t.l.c.) as the acidic material [(29), (35)] previously obtained.

The overall yield of impure bicyclic ketone (13) was 16.5%.

Properties and reactions of the acidic material from acid treatment of the diketone (16) [p. 221].

The acidic material was distilled to a yellow viscous oil, b.p. 150-154°/0.15-0.2 mm. (Found: C, 77.7; H, 7.6. $C_{14}H_{16}O_2$ requires C, 77.8; H, 7.5%). The oil became a glass on cooling but did not solidify. The i.r. spectrum (carbon tetrachloride) showed carboxylic acid absorptions ν_{OH} at 3544-3518 cm^{-1} (ϵ 46; $\Delta\nu_{\frac{1}{2}}$ 26 cm^{-1}) and ν_{CO} at 1756 cm^{-1} (ϵ 194; $\Delta\nu_{\frac{1}{2}}$ 17 cm^{-1}; monomer) and 1707 cm^{-1} (ϵ 563; $\Delta\nu_{\frac{1}{2}}$, 14 cm^{-1}; dimer). The u.v. spectrum showed λ max 250 mμ (logϵ, 3.98). T.l.c. of the acidic material indicated the presence of only one compound.

On <u>esterification</u> with anhydrous methanol and concentrated sulphuric acid, the acidic material (4.15g.) gave a neutral product (3.41g.; 75%) which distilled to a yellow oil, b.p. 134°/0.1 mm. (Found: C, 78.61; H, 8.06. $C_{15}H_{18}O_2$ requires C, 78.23; H, 7.88%), ν_{CO} 1730 cm^{-1}. T.l.c. showed only one spot, but g.l.c. (1% polyethyleneglycol adipate, 150°) showed two peaks (R.T. = 324, 360 secs. respectively) indicating that the material was a mixture of <u>esters</u>. The acidic material was therefore presumed to be a mixture of two acids [(29), (35)].

<u>Attempted decarboxylation of the acidic material [(29), (35)]</u>.

(a). <u>Soda-lime</u>:- distillation of the acidic material from soda-lime at 0.1 mm. gave unchanged starting material accompanied by a small amount of a neutral solid identified (i.r.) as the lactone (40).

(b). <u>Copper powder/quinoline</u>:- the acidic material (2g.) was heated under reflux for 12 hours in quinoline (20 ml.)

containing copper powder.

The cooled mixture was filtered and the filtrate diluted with ether. Separation of the product into acidic and neutral fractions was effected by extraction. The acidic fraction consisted of unchanged starting material (1.6g.). The neutral material (44 mg.) was an intractable oil which was not identified.

(c) Diphenyl ether:- a solution of the acidic material (4g.) in diphenyl ether (30 ml.) was heated under reflux for 3 hours, with considerable darkening. The solution was diluted with ether, washed with aqueous sodium carbonate, with brine and dried. The basic extract afforded unchanged starting material (2.57g.). The neutral ethereal solution gave a viscous oil (1.2g.) whose i.r. spectrum showed contamination with diphenyl ether. Chromatography on silica separated the product from the diphenyl ether. The product was shown (t.l.c.) to contain at least eleven different compounds. No clear-cut separation was achieved and the mixture could not be separated. One of the components was tentatively identified (t.l.c.) as the lactone (40).

Reduction of the acidic material [(29), (35)].

The acidic material (310 mg.) in ethyl acetate was hydrogenated using 5% palladium-charcoal as catalyst. The uptake of hydrogen was 36.5 ml. at 18° (Theoretical uptake for 1 molar equivalent = 32 ml. hydrogen at N.T.P.). Filtration and concentration of the filtrate gave a saturated acid (36) (370 mg.; quant.), recrystallised from light petroleum (b.p. 40-60°) as white needles, m.p. 57-59° (Found: C, 76.7 ; H, 7.8 ; $C_{14}H_{18}O_2$ requires C, 77.0 ; H, 8.3 %). The i.r. spectrum showed carbonyl absorption at 1700 cm^{-1} and reduced intensity of aromatic absorptions. The u.v. spectrum showed λ_{max} 242-243mμ

Decarboxylation of the saturated acid (36)[117].

Decarboxylation of the acid (8g.) from the above reaction was effected by boiling under reflux for 72 hours in quinoline (28g.) containing copper powder (2g.). The mixture was filtered, the filtrate dissolved in ether, washed with dilute hydrochloric acid, aqueous sodium hydroxide (4N) and brine and dried. Concentration of the ethereal solution gave an oil which was chromatographed on alumina to yield phenylcycloheptane (200 mg.; 3%) b.p. 110-112°/10 mm., identical (i.r., n.m.r., t.l.c.) with an authentic sample prepared by standard methods[131,132].

Attempted cyclisation of the saturated acid (36).

A solution of the acid (36) (200 mg.) in polyphosphoric acid (5 ml., commercial grade) was warmed (steam-bath) with stirring for 1 hour. The dark brown solution was poured, while still hot, onto crushed ice and left to stand overnight.

The mixture was then extracted and the ethereal extract washed with aqueous sodium hydrogen carbonate, with brine, and dried. Removal of solvent from the neutral ethereal extract gave a yellow oil (167 mg.; 91%) with a distinctive odour. The i.r. spectrum of the crude material showed sharp carbonyl absorption at 1670 cm^{-1} and an intense peak at 1590 cm^{-1}. The usual bands at 690, 750 cm^{-1} for a monosubstituted benzene were absent and aromatic substitution bands appeared at 800, 775, 750, 730 cm^{-1}. The u.v. spectrum showed λ_{max} 250 mμ.

A sample of the product readily gave an orange precipitate with an acidic solution of 2:4-dinitrophenylhydrazine. The m.p. of the crude material indicated that it was a mixture. Chromatography of the derivative on 4:1 bentonite-kieselguhr gave two fractions:-

1. A mixture of a yellow and an orange solid which sublimed at 210-220°, m.p. 235-255°. This material was discarded.
2. An orange solid which sublimed at 220°; m.p. 245°. It was further purified by sublimation at 160°/0.2 mm., giving two separate sublimates
   (a) A solid, m.p. 82°, obtained in an amount which precluded any further investigation.
   (b) Orange, diamond-shaped plates which sublimed at 253°, m.p. 259-260°. Insufficient material was available for analysis but mass-spectrometry showed a parent peak at 380 mass units ($C_{20}H_{20}N_4O_4^{+}$).

Attempted permanganate oxidation of the acidic material [(29), (35)].

(a) A solution of the acidic material (1.08g.) in water (25 ml.) containing sodium hydroxide (0.5g.) was warmed to 80° and treated, dropwise, with a saturated aqueous solution of potassium permanganate until a faint permanent colouration was obtained in the supernatant layer. The reaction was worked up in the usual way but on acidification, no precipitate was obtained. Extraction of the acidified solution with ether gave a yellow solid, recrystallised from light petroleum as white needles, m.p. 118-122°. The material was identical (i.r., mixed m.p.) with a sample of benzoic acid.

(b) To a refluxing solution of the acidic material [(29), (35)] (7g.) in acetone (100 ml.) was added, dropwise, a solution of potassium permanganate (4g.) in acetone (100 ml.). Heating was continued for 1 hour. Manganese dioxide was reduced with sulphur dioxide, causing precipitation of an oil which was extracted into ether and separated into acidic and neutral components. The acidic fraction was a brown oil (3.1g.) shown (i.r., t.l.c.) to be predominantly unchanged starting material. The neutral fraction was an orange viscous oil (2.91g.) whose i.r. spectrum showed only weak hydroxyl absorption and a broad unresolved carbonyl band. T.l.c. examination of the material showed between eight and ten indistinct spots, several of which were demonstrated to contain carbonyl functions. The mixture was not separated.

Ozonolysis

(a). Reductive work-up:- a solution of redistilled acidic material [(29), (35)] (2g.) in methylene chloride (50 ml.) was cooled to -70°. Ozone was bubbled through the solution at a rate of 50 ml./minute, until the typical blue colouration of excess ozone appeared (30 minutes). The solution was allowed to come to room temperature and powdered zinc (2g.) and glacial acetic acid (15 ml.) added with stirring. After 1 hour a negative starch-iodide test was obtained. The zinc was filtered off, washed with methylene chloride and the combined filtrate and washings evaporated to give a yellow oil (1.64g.) containing some solid. Trituration did not effect any separation of solid material nor was the whole induced to solidify. The i.r spectrum of the crude material showed acidic hydroxyl absorption and a broad, partly resolved carbonyl band (ν_{CO} ca. 1740 1715, 1680 cm^{-1}).

The crude material was not purified but was oxidised with Jones's reagent[84] in the usual way. As solvent was removed by evaporation from an ethereal extract of the product, a white solid crystallised out. This was removed by filtration. Both it and the filtrate were examined separately. The solid melted over a considerable range of temperature. Insolubility in most organic solvents prevented purification by recrystallisation while strong adsorption on silica and alumina prohibited chromatographic purification. The crude material gave an or orange precipitate with Brady's reagent[102] and its i.r. spectrum showed carbonyl absorptions at 1725 (sh), 1715, 1685 and 1675 cm^{-1}. The *filtrate* on evaporation gave an oil, t.l.c. examination of which showed three strongly adsorbed spots near the origin. The i.r. spectrum showed hydroxyl and unresolved carbonyl absorptions.

(b). *Oxidative work-up*:- a solution of the acidic material [(29), (35)] (5g.) in methylene chloride (60 ml.) was cooled to -70° and a stream of ozone bubbled through the solution until excess was present. The solution was allowed to come to room temperature and was added dropwise to a hot (45°) solution of 30% hydrogen peroxide (50 ml.). Addition was completed in 1.5 hours and during this time the temperature was kept between 40-60°, cooling if necessary. The mixture was then stirred at room temperature overnight, methylene chloride (15 ml.) added and the mixture heated under reflux for 1 hour. Methylene chloride was distilled off slowly and the residue extracted with ether. A sample taken at this point from the ethereal extract showed the product to be a mixture of six compounds (t.l.c.). The ethereal extract was washed with aqueous ferrous sulphate (forming a brown curdy *precipitate* insoluble in both layers), sodium hydrogen carbonate, brine and dried. The neutral ethereal solution gave a red oil (0.6g.) shown by t.l.c. to be a mixture of two compounds. The i.r. spectrum showed hydroxyl absorption at 3500 cm^{-1} unlike that of a typical carboxylic acid, and carbonyl absorptions at 1865, 1775, 1735 and 1685 cm^{-1}. The mixture was not separated.

Acidification of both the precipitate and the alkaline extract afforded the same product, a yellow semi-solid (4.17g. combined), shown (t.l.c.) to be a mixture of four compounds. A partial separation was achieved by solubility differences in ether. The ether-soluble portion consisted of a mixture of three compounds which were not further separated or identified. The ether-insoluble solid was removed by filtration, washed with ether and dried, white needles, m.p. 165-170°. Initial t.l.c. examination (silica; 15% ethyl acetate light petroleum) showed only one spot but further investigation (silica, benzene dioxan:acetic acid, 90:25:4 by volume) showed that three materials were actually present. Insolubility of the product prevented purification by recrystallisation but repeated washing with ether gave a white crystalline solid, m.p. 166-170°, ν_{CO} 1702, 1692 cm^{-1}. The solid gave an orange-yellow precipitate with Brady's reagent^{102}. The derivative was very soluble in methanol.

Esterification of the solid (101.2 mg.) in methanol with an ethereal solution of diazomethane gave a yellow oil (96 mg.; 85%), ν_{CO} 1730 and 1690 cm^{-1}. T.l.c. of the ester showed three spots, with very similar R_f values. Distillation did not effect any separation of the mixture. Thick-plate chromatography (silica, 1 mm.; 30% ethyl acetate-light petroleum) proved unsuccessful and no pure material was obtained. An anhydride of the solid (m.p. 166-170°) was formed by warming the crude solid (64 mg.) with acetyl chloride (5 ml.) for 3 hours. Excess of acetyl chloride was removed by distillation, the residue diluted with water and extracted with ether. The washed and dried ethereal solution gave a solid anhydride (32) (51 mg.), recrystallised from benzene-light petroleum as white needles, m.p. 100-101° (Found: C, 68.52; H, 5.58. $C_{14}H_{14}O_4$ requires C, 68.28; H, 5.73%). The i.r. spectrum (carbon tetrachloride) showed carbonyl absorptions at 1863 and 1794 cm^{-1} (anhydride of the succinic type) and at 1692 cm^{-1} (aryl ketone). The n.m.r. spectrum (deuterochloroform) showed the following signals:- multiplet at 2.03τ(2H, aromatic protons adjacent to carbonyl), multiplet at 2.4τ(3H, aromatic protons) multiplet at 6.9τ(5H, protons adjacent to carbonyls), unresolved band at 8.1 τ (4H, methylene protons).

Attempted bromolactonisation of the acidic material.

(a) The acidic material [(29), (35)] (1.5g.) dissolved in the minimum volume of acetic acid was cooled in ice. A solution of bromine in acetic acid was added dropwise, with cooling, until excess of bromine was present. The reaction mixture was allowed to stand at room temperature for 1 hour then neutralised with aqueous sodium hydroxide (4N). The solution was filtered, the filtrate acidified and extracted with ether and chloroform. Both organic extracts were washed (brine) and dried. The ether extract gave a yellow viscous oil, shown (t.l.c.) to be a mixture of at least four compounds. The chloroform extract gave a black tarry oil. The material from both extracts was not further examined.

(b) Bromine was added dropwise to a solution of the acidic material [(29), (35)] in aqueous sodium hydroxide (4N) until excess was present. The reaction mixture was extracted with ether, the residual aqueous layer acidified and extracted with chloroform. Both extracts were washed and dried in the usual way. The ether extract gave a yellow oil. T.l.c. showed only one spot with an R_f value equal to that of the lactone (40). The i.r. spectrum, however showed hydroxyl absorption at 3500 cm^{-1} and carbonyl absorption at 1780 cm^{-1} (sh) 1750 cm^{-1} and 1730 cm^{-1} (sh). The oil could not be induced to crystallise.

The chloroform extract yielded a low-melting solid which could not be recrystallised. T.l.c. showed it to be a mixture of four compounds. The mixture was not separated.

Attempted iodolactonisation[134] of the acidic material.

A solution of the acidic material [(29), (35)] (8.6g.) in aqueous sodium hydrogen carbonate (240 ml., 0.5M) was treated with iodine (20.1g.) in a solution of potassium iodide (40g.) in water (120 ml.). The reaction mixture was allowed to stand at room temperature for 48 hours with exclusion of light. A thick tarry deposit developed. The mixture was extracted with methylene chloride and the organic and aqueous layers separated with difficulty. The organic layer was washed with aqueous sodium thiosulphite (0.1N), brine and dried. Concentration of the extract gave a dark green oil (9g.) which was redissolved in chloroform. The chloroform solution was washed with sodium thiosulphite, extracted with aqueous sodium carbonate and sodium hydrogen carbonate and dried. Acidification and extraction of the basic extracts gave a brown oil (0.9g.) which foamed under reduced pressure to give a yellow solid, m.p. (crude) 130°. Attempted recrystallisations of the solid resulted in sticky oils. The material gave a positive Beilstein test. The neutral chloroform extract gave an iodine-containing brown oil (6.1g.) which did not solidify. A sample (2g.) was chromatographed on silica (50g.) and considerable decomposition occurred, both neutral and acidic materials being eluted. A successful separation was not achieved, the fractions exhibiting much overlap.

Lactonisation of the acidic material.

(a) Acetic acid/hydrochloric acid:- a solution of the acidic material [(29), (35)] in glacial acetic acid (30 ml.) and concentrated hydrochloric acid (6 ml.) was heated under reflux for 8 hours. The product was separated into acidic and neutral fractions. The acidic fraction (1.6g.) was identified (i.r., t.l.c.) as unchanged starting material. The neutral fraction (1.11g.) consisted of an oil containing some solid. T.l.c. of the crude product showed two main spots, one at the position of the known lactone (40) and the other with an R_f value corresponding to that of the bicyclic ketone (13). The i.r. spectrum showed characteristics of both these compounds. On redissolving the crude product in ether, there remained a white solid residue which was removed by filtration. Recrystallisation from light petroleum gave a white crystalline solid m.p. 117-120° whose i.r. spectrum was superposable on that of the lactone (40) except for a shoulder on the carbonyl band at 1745 cm^{-1} which was not removed by further recrystallisation.

(b) 50% aqueous sulphuric acid/acetic acid:- a solution of the acidic material [(29), (35); lactone-free (t.l.c.)] (2g.) in glacial acetic acid (30 ml.) and 50% aqueous sulphuric acid (15 ml.) was heated under reflux for 8 hours. Excess of acetic acid was removed under reduced pressure, the residue flooded with water and extracted with ether. The ethereal solution was washed with aqueous sodium carbonate, with brine and dried. Acidification of the basic extract followed by ether extraction gave a viscous brown oil, (1.77g.) shown (i.r., t.l.c.) to be unchanged starting material. The neutral ether, on evaporation, gave a yellow solid (192 mg.) which was recrystallised from light petroleum as white needles, m.p. 115-120°, identical (i.r. mixed m.p.) with the lactone (40). T.l.c. showed one spot with an R_f value equal to that of the lactone (40).

Properties and reactions of the lactone (40) from acid treatment of the diketone (16) [p.221].

The lactone (40) was recrystallised from light petroleum (b.p. 80-100°) as white needles, m.p. 121°. Further purification was effected by solution in methanol and treatment with an aqueous solution of sodium borohydride. The reaction was worked up in the usual way and the product chromatographed on silica (20:1 by weight). Elution with light petroleum gave a small amount of a yellow oil which was discarded, followed by the pure lactone (40), m.p. 122° (Found: C, 78.02; H, 7.74. $C_{14}H_{16}O_2$ requires C, 77.8; H, 7.5%). The i.r. spectrum (carbon tetrachloride) showed ν_{CO} at 1780 cm^{-1} (ϵ, 90; $\Delta\nu_{\frac{1}{2}}$ 12.5 cm^{-1}) and ν_{C-O} at 1150 cm^{-1}. The n.m.r. spectrum (deuterochloroform) showed $-CO-\overset{|}{\underset{|}{C}}-H$ as a doublet at 5.1τ (1H, J = 6.9 cps) with barely discernable sub-splitting.

Attempted hydrolysis of the lactone (40).

(a) 10% aqueous sodium hydroxide:- a solution of the lactone (40) (200 mg.) in 10% aqueous sodium hydroxide (25 ml.) (containing sufficient ethanol to effect solution) was heated under reflux for 3 hours. Extraction of the reaction mixture with ether gave unchanged lactone (40) (167 mg.). Acidification and extraction of the alkaline solution afforded a yellow waxy material (20 mg.) which was oxidised with Jones's reagent[84]. The product, a yellow oil, gave an orange precipitate with Brady's reagent[102]. Lack of material prevented purification and identification of the oil whose i.r. spectrum did however show hydroxyl and carbonyl absorptions (ν_{OH} 3400 cm^{-1}; ν_{CO} ca. 1700 cm^{-1}).

(b) 35% aqueous sodium hydroxide:- the lactone (40) (167mg.) was dissolved in the minimum volume of ethanol and 35% aqueous sodium hydroxide added (20 ml.). The mixture was heated under reflux for 2 hours and allowed to stand at room temperature for 48 hours. The alkaline solution was extracted with ether, occasioning precipitation of a white solid at the interface. It was removed by filtration. (A). The ethereal solution was washed and dried (B). The aqueous layer was acidified, giving a white precipitate which was extracted into ether and the ethereal solution washed and dried (C).

The solid (A) was water-soluble; its i.r. spectrum showed strong hydroxyl absorption (ν_{OH} 3400 cm^{-1}) and two bands at 1550 and 1420 cm^{-1} (carboxylate anion). Oxidation of the solid with chromium trioxide in pyridine[135] gave a white crystalline solid identical (i.r.) with the lactone (40).

Extracts B and C both yielded the starting lactone (40).

(c) Sodium hydroxide/methyl iodide:- the lactone (40) (5g.; 0.02 mole) was dissolved in 0.1N sodium hydroxide (200 ml.; 1 molar equivalent) containing methanol (10 ml.). The solution was heated under reflux for 28 hours and allowed to stand at room temperature for 24 hours. The solution was evaporated to dryness under reduced pressure, the residue washed with ether, then dried by azeotroping with benzene. The dry, powdered residue was suspended in Analar acetone and treated with redistilled methyl iodide (30g.). The mixture was heated under reflux for 2 hours, and excess of acetone and methyl iodide distilled off to leave a yellow solid (m.p. 75-80°; crystals appeared at 140°, remelting at 240°). The i.r. spectrum was similar to that of the lactone (40), with addition bands at 3400 and 1620 cm^{-1}. T.l.c. (20% ethyl acetate-light petroleum) showed only one spot with an R_f value equal to that of the lactone (40). A mixture of the product and the lactone (40) also showed only one spot. Recrystallisation of the product from light petroleum gave a solid, m.p. 120-121°, identical with the lactone (40).

Lithium aluminium hydride reduction of the lactone (40).

To a stirred suspension of lithium aluminium hydride (300 mg.) in dry tetrahydrofuran (15 ml.) was added a solution of the lactone (40) (2g.) in dry tetrahydrofuran (20 ml.) over 2 hours. The mixture was heated under reflux for 5 hours. Excess of lithium aluminium hydride was destroyed by careful addition of saturated ammonium sulphate followed by sufficient dilute hydrochloric acid to dissolve the lithium salts. The bulk of the solvent was removed under reduced pressure, the residue diluted with water and extracted with ethyl acetate. The organic layer was washed, dried and concentrated to give a yellow sticky oil (2.2g.) which solidified on cooling. T.l.c. showed the material to consist of three compounds, one of which was the starting lactone (R_f value). Repetition of the reduction with a reflux time of 7.5 hours gave a sticky solid identical to the first except that it no longer contained any starting lactone (40). Recrystallisation of the product (now shown by t.l.c. to be a mixture of two compounds) proved exceedingly difficult and generally resulted in oils or soft solids. A sample of impure diol (45) was eventually obtained by successive recrystallisations from water as a white solid, m.p. 80-85^o (Found: C, 75.23; H, 8.45. $C_{14}H_{20}O_2$ requires C, 76.33; H, 9.15%). The n.m.r. spectrum (deuterochloroform) of the impure sample showed a poorly resolved multiplet (1H) centred at 5.98 τ

(assigned to proton of a secondary alcohol $-C\underline{H}OH$) and a doublet (2H) at 6.54 τ (J = 5 cps; assigned to methylene protons of a primary alcohol, $-O-\underline{CH_2}-\overset{/}{\underset{\backslash}{C}}H$). In dimethylsulphoxide, the secondary and primary hydroxyl protons were observed respectively as a doublet at 5.78 τ (J = 4.8 cps), and a **triplet** at 5.5 τ (J = 4.8 cps), each (1H).

Acetylation of the diol (45) with acetic anhydride in pyridine gave a yellow oil which did not solidify. The i.r. spectrum showed absence of hydroxyl absorption, a broad carbonyl band at 1738 cm^{-1} (C = O of acetate) and strong absorption at 1248 cm^{-1} (C - O of acetate). Attempted crystallisation and prolonged standing gave rise to the presence of a hydroxyl function. T.l.c. showed the product to be a mixture.

Benzoylation of the diol (45) in aqueous base, with benzoyl chloride gave a yellow oil, shown by t.l.c. to be a mixture of three compounds, none of which was identical with the starting material. The oil could not be induced to solidify and the presence of solvents only appeared to hasten decomposition. The i.r. spectrum of the crude product showed a strong carbonyl band at 1718 cm^{-1} (C - O of benzoate ester), bands at 1283 and 1120 cm^{-1} (C - O of benzoate ester) as well as a broad, intense hydroxyl band at 3500 cm^{-1}. On prolonged standing of the material, the intensity of the hydroxyl band in the i.r. spectrum increased at the expense of the carbonyl band.

Attempted oxidation of the diol (45).

(a) The impure diol (45) (500 mg.) in Analar acetone (10 ml.) was cooled to 0° and treated with Jones's reagent[84] until colour persisted in the supernatant layer. The mixture was warmed to coagulate the chromium (III) salts and worked up in the usual way. The product, a yellow oil was a mixture of four compounds; the i.r. spectrum showed hydroxyl absorption and a broad unresolved carbonyl band (1760-1680 cm^{-1}).

(b) A solution of the impure diol (45) (500 mg.) in acetone at 15^{o} was treated with excess of Jones's reagent and worked up in the usual way to give a semi-solid. On attempted solution of the material in ether, a crystalline residue was obtained. This was removed by filtration and recrystallised from ether as white needles, m.p. 114°, identical (i.r.; mixed m.p.) with a sample of the di-addition product [(20) or (21)], Concentration of the filtrate gave a yellow oil, similar to the mixture obtained in (a). The i.r. spectrum showed hydroxyl absorption and a broad unresolved carbonyl band (ca. 1740-1680 cm^{-1}). T.l.c. showed three spots. The oil gave a precipitate with Brady's reagent[102]. On standing, the oil was observed to deteriorate (t.l.c. showed ten spots) and was rejected.

2-Phenylbicyclo-[3:2:1]-oct-2-en-8-one (13).

The bicyclic ketone (13) was prepared by the method used for the analogous ketone (14), method (b) [p. 217]. The product obtained from cyclisation of the diketone (16) (12g.) was a brown mobile oil (11g.) shown by t.l.c. examination to be a mixture of three compounds. Chromatography of the mixture on silica (230g.) caused decomposition and several materials were eluted from the column. These included:-

1. A yellow oil (104 mg.; 1.2% of total recovered material), eluted with light petroleum. The oil possessed an ester-like odour, was t.l.c. pure and showed ν_{CO} at 1738 cm^{-1}.
2. A white crystalline solid (5.82g.; 68% of the total) eluted with 10-15% ethyl acetate-light petroleum. The required bicyclic ketone (13) was recrystallised from benzene-light petroleum as needles, m.p. 71-75° and 89-93° (Found: C, 85.06; H, 7.13. $C_{14}H_{14}O$ requires C, 84.81; H, 7.12%). The i.r. spectrum (carbon tetrachloride) showed ν_{CO} at 1758 cm^{-1} (ϵ 548). Three small bands were also present at 3085, 3064 and 3030 cm^{-1} (ϵ, 22.6; 28.3; 39.6 respectively). The n.m.r. spectrum (deuterochloroform) showed:-

   multiplet at 2.6 τ (5H, aromatic protons), triplet at 4.1 τ (J = 3.75 cps; 1H, olefinic proton), multiplet centred on 7.2 τ and multiplet centred on 7.85 τ (8H combined).

   The ketone (13) gave a yellow 2:4-dinitrophenylhydrazone, m.p. 70-73°.
3. A brown oil (2.54g.; 30%) eluted (from methanol) with 20% ethyl acetate-light petroleum. T.l.c. showed the oil

to be a mixture of five compounds one of which was identified (R_f value) as the diketone (16).
The overall yield of the required bicyclic ketone (13) was 52.8%.

Reduction of the bicyclic ketone (13).

The bicyclic ketone (13) (280 mg.) in ethyl acetate (25 ml.) was hydrogenated over 5% palladium-charcoal as catalyst. The uptake of hydrogen was 36 ml. at 18° (1 molar equivalent of hydrogen = 31.6 ml. at N.T.P.). Filtration and concentration of the filtrate gave a colourless oil (270 mg.), ν_{CO} 1735 cm^{-1}. The oil gave a yellow 2:4-dinitrophenylhydrazone which was chromatographed on 4:1 bentonite-kieselguhr. Elution with chloroform gave the yellow derivative, recrystallised from methanol as needles, m.p. 72-75°. On admixture with the 2:4-dinitrophenylhydrazone of the unsaturated bicyclic ketone (13) (m.p. 70-73°), a depression of m.p. was observed.

Attempted borohydride reduction of the bicyclic ketone (13).

The ketone (13) (345 mg.) in methanol (25 ml.) was treated with a solution of sodium borohydride (200 mg.) in water (10 ml.). The mixture was allowed to stand overnight at room temperature, diluted with water and extracted with ether (A). The residual aqueous layer was acidified and extracted with ether (B). Both extracts were washed and dried. Extract A gave a yellow oil (410 mg.) shown by t.l.c. (18% ethyl acetate-light petroleum) to be a mixture of two compounds, one of which was identified (R_f value) as the diketone (16). The mixture was not separated. The i.r. spectrum of the crude material consisted of broad absorption bands in both hydroxyl and carboxyl regions. Extract B gave a yellow oil (20 mg.) whose R_f value (18% ethyl acetate-light petroleum) was identical with that of the diketone (16).

Reactions of the bicyclic ketone (13) in acidic, basic and neutral media. see Table III.

(a) Sulphuric acid/dioxan.

A solution of the bicyclic ketone (13) (228 mg.) in dioxan (25 ml.) and concentrated sulphuric acid (0.1 ml.) was heated under reflux for 2.5 hours. The mixture was poured into water and extracted with ether. The ethereal solution was washed with brine, aqueous sodium carbonate and brine again till the washings were neutral. Removal of solvent from the ether extract left a yellow oil (162 mg.) shown by t.l.c. to be a mixture of the ketone (13) and the lactone (40). The sodium carbonate extract on acidification and extraction with ether gave an oil (50 mg.) identical (i.r., t.l.c.) with the acidic material [(29), (35)].

(b) Sodium hydroxide/dioxan.

A solution of the bicyclic ketone (13) (142 mg.) in dioxan (25 ml.) and aqueous sodium hydroxide (10 ml.; 4N) was heated under reflux for 2.5 hours. The reaction mixture was washed with ether and the ethereal solution washed (brine) and dried. Removal of the solvent left a yellow oil (10 mg.) shown by t.l.c. to be a mixture of the bicyclic ketone (13) and a small amount of the lactone (40) or the diketone (16). The i.r. spectrum of the material, however, showed only the single carbonyl peak (1755 cm^{-1}) of the sodium hydroxide solution gave a yellow oil (50 mg.) whose i.r. spectrum indicated that it was the acidic material [(29), (35)]. T.l.c. confirmed this.

(c) Water/dioxan.

A solution of the bicyclic ketone (13) (267 mg.) in dioxan (25 ml.) and water (5 ml.) was heated under reflux for 2.5 hours. The reaction mixture was diluted with water and extracted into ether. It was then worked up as in (a). The neutral product (127 mg.) was a mixture of starting ketone (16) and the lactone (40) (i.r., t.l.c.). The acidic fraction was a yellow oil (75.4 mg.), identical (i.r., t.l.c.) with the acidic material [(29), (35)].

(d) Acetic acid/hydrochloric acid.

A solution of the ketone (13) (69.5 mg.) in glacial acetic acid (10 ml.) and concentrated hydrochloric acid (0.1 ml.) was heated under reflux for 2.5 hours. The reaction was worked up in the usual way. The neutral material obtained was a semi-solid (20 mg.) whose i.r. spectrum showed unresolved carbonyl absorption ca. 1745 cm^{-1} but no lactone carbonyl absorption. The acidic product was a yellow oil (20 mg.) identical with the acidic material [(29), (35)].

(e) Water.

The bicyclic ketone (13) (81.8 mg.) was suspended in water and the two-phase system heated under reflux for 3.3 hours. The reaction mixture was extracted with ether and the product separated into neutral and acidic fractions. The weak i.r. spectrum of the neutral fraction (4 mg.) corresponded to that of the starting ketone (13). The acidic fraction of the product, a yellow oil (50 mg.) gave a poorly resolved i.r. spectrum, similar to that of the acidic material [(29), (35)].

Preparation of indeno (2',3':3,2) bicyclo-[3:2:1]-oct-2-en-8-one (58) and related compounds.

Phenylsuccinic anhydride.

This anhydride was prepared by warming phenylsuccinic acid in acetic anhydride for 2 hours. Excess of acetic anhydride was removed under reduced pressure and the residue dissolved in ether. The ethereal solution was washed rapidly with aqueous sodium hydrogen carbonate, with brine and dried. Evaporation of the ethereal solution gave a 70% yield of the anhydride, long white needles, m.p. 54° (from ether). i.e. d, l and racemic forms were present.

1-keto-3-carboxyindane (50) and α-hydrindone (51)[136].

Sherif's method[136] for the preparation of the acid (50) was followed. Treatment of phenylsuccinic anhydride with aluminium chloride in o-dichlorobenzene gave the required keto-acid (50) as its monohydrate, m.p. 85°. Drying over phosphorus pentoxide gave the acid (50) itself, m.p. 116-118°.

The crude keto-acid (51) (4g.) was heated under reflux for 1 hour with redistilled quinoline (30 ml.) and copper bronze (1g.). The cooled, filtered mixture was extracted with benzene and the organic extract washed with dilute hydrochloric acid and brine, dried and concentrated to give a brown oil (1.5g.; 50%). The oil was shown (t.l.c.) to be a mixture of four compounds. It was therefore dissolved in chloroform, washed with aqueous sodium carbonate and brine and dried to give a brown oil (0.4g.) which solidified on cooling. T.l.c. examination of the oil showed it to be a mixture of two compounds. Recrystallisation from light petroleum (5X) gave a very small amount of a yellow crystalline solid, m.p. 35-40°. This was shown by comparison (i.r., t.l.c.,) of a later sample to be impure α-hydrindone (51).

α-Hydrindone (51).

β-Phenylpropionic acid (49) (50g.) and commercial grade polyphosphoric acid (500g.) were heated together (steam-bath), with stirring, for 1 hour. The hot reaction mixture was poured onto crushed ice (1 Kg.) and extracted with ether and with ethyl acetate. The combined extracts were washed with brine, with aqueous sodium hydrogen carbonate, with brine again and dried. Acidification and extraction of the sodium hydrogen carbonate extract gave unchanged starting material (49) (0.74g.). Concentration of the organic extracts gave a yellow oil (43g.) which sodidified on cooling. The crude material was exhaustively steam-distilled. The distillate, on cooling, deposited α-hydrindone (51) as white glistening plates m.p. 42°. The yield of product, collected by filtration, was 32.4g. (73%). The residue from steam-distillation contained a water-insoluble solid (9.2g.) which was recrystallised from ethyl acetate as bright yellow needles, m.p. 144-146°. (Found: C, 87.70; H, 5.78. $C_{18}H_{14}O$ requires C, 87.78; H, 5.73%). Mass-spectrometry showed a parent ion at 246 mass units ($C_{18}H_{14}O^+$). The i.r. spectrum showed carbonyl absorption at 1670 cm^{-1}, double bond absorption at 1610 cm^{-1} and ortho substitution of an aromatic ring (750 cm^{-1}). The solid {postulated as 2-(hydrindylidene-1)-α-hydrindone (52)] turned brown on standing. It gave an unstable 2:4-dinitrophenylhydrazone.

The Mannich base of α-hydrindone.

A solution of α-hydrindone (51) (24g.; 0.18 mole), paraformaldehyde (11.4g.; 0.23 mole) and dimethylamine hydrochloride (16.2g.; 0.23 mole) in absolute ethanol (100 ml.) and concentrated hydrochloric acid (3 ml.) was heated under reflux for 2 hours. The mixture was cooled slightly, poured into acetone and allowed to stand overnight in the cold. The white crystalline precipitate (30.5g.) was filtered off and the mother liquors concentrated to give a further crop of 3.5g. (yield 86%). The Mannich base hydrochloride was recrystallised from absolute ethanol-acetone mixtures (1:4 by volume) as white needles, m.p. 148-150°. (Found: C, 63.63; H, 7.36; N. 6.07. $C_{12}H_{16}NOCl$ requires C, 63.84; H, 7.12; N, 6.21%). The solid was hygroscopic and was stored in a vacuum desiccator over silica gel.

Liberation of the free Mannich base from its hydrochloride in the usual way with aqueous sodium hydroxide gave the free base in an impure state in 10% yield. A more satisfactory method consisted of treating an aqueous solution of the Mannich base hydrochloride with 1 molar equivalent of 5% ammonium hydroxide. The resultant precipitate was extracted into ether, washed with brine and dried. Concentration of the ethereal solution gave the free base in 35% yield.

β-(2-oxocyclopentylmethyl)-α-hydrindone (54).

The crude Mannich base (18.9g.; 0.1 mole) prepared as above, and redistilled cyclopentanone (25.2g.; 0.3 mole) were heated together at reflux temperature for 40 minutes. The reaction was worked up in the usual way. Distillation of the product gave three fractions:-

1. a yellow oil (4.1g.), b.p. 146-148°/0.07 mm., which partially solidified on cooling. T.l.c. showed two spots.
2. a yellow oil (5.4g.), b.p. 164-176°/0.07 mm., which solidified on cooling. T.l.c. showed two spots.
3. a yellow oil (9.5g.), b.p. 176°/0.07 mm., which solidified on cooling. T.l.c. showed two almost coincident spots.

Recrystallisation of fractions 1 and 2 gave solids of indefinite m.p. but repeated recrystallisation of fraction 3 from light petroleum gave the required diketone (54) (t.l.c. pure) as a white solid, m.p. 60-64°. (Found: C, 78.72; H, 6.97. $C_{15}H_{16}O_2$ requires C, 78.92; H, 7.06%); the i.r. spectrum showed a poorly resolved carbonyl band ca. 1740-1680 cm^{-1}.

Reaction of the diketone (54) with acetic acid/hydrochloric acid.

The reaction was carried out as previously, a solution of the diketone (54) (3g.) in glacial acetic acid (25 ml.) and concentrated hydrochloric acid (6 ml.) being heated under reflux for 8 hours. The reaction was worked up in the usual way. The neutral fraction of the product was a yellow oil (0.6g.). T.l.c. showed three overlapping spots, one of which corresponded (R_f value) to the starting diketone (54). The mixture was not separated.

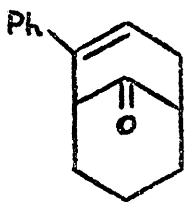
The acidic fraction of the product was a white solid (2.1g.; 70%). Recrystallisation of the solid several times from chloroform-light petroleum mixtures and finally from light petroleum (b.p. 80-100°) gave a white crystalline solid, observed to melt at 158-160° then remelt at 168-169°. T.l.c. showed the solid to be only one compound, the acid (55). (Found: C, 78.86; H, 7.13. $C_{15}H_{16}O_2$ requires C, 78.92; H, 7.04%), ν_{CO} ca. 1700 cm^{-1}. The n.m.r. spectrum (deuterochloroform) showed complete absence of olefinic protons. The methylene protons of the indene ring were observed as a singlet at 6.65τ (2H). No other individual signals were distinguishable in the broad bands centred at 7.27τ and 8.0τ.

The acid (55) (500 mg.) was heated under reflux for 24 hours in glacial acetic acid (10 ml.) and concentrated hydrochloric acid (1 ml.). The reaction was worked up in the usual way. The acidic fraction of the product was unchanged starting material (489 mg.). The neutral fraction was an oil (0.6 mg.; 0.0001%). T.l.c. showed one faint spot whose R_f value differed from that of the diketone (54).

Indeno(2',3':3,2)bicyclo-[3:2:1]-oct-2-en-8-one (58).

Treatment of the diketone (54) (3g.) with p-toluenesulphonic acid in dry benzene as for the other bicyclic ketones gave an orange oily solid (2g.; 72.4%) shown by t.l.c.

to be one compound. Trituration with ether gave a white solid which was filtered off, washed with ether and recrystallised from light petroleum. This gave the required bicyclic ketone (58) as fine white needles, m.p. 137° (Found: C, 85.65; H, 6.92. $C_{15}H_{14}O_3$ requires C, 85.69; H, 6.71%), ν_{CO} nujol 1745 cm^{-1}. The n.m.r. spectrum (deuterochloroform) showed complete absence of olefinic protons.



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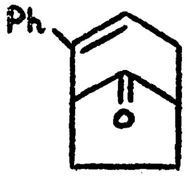

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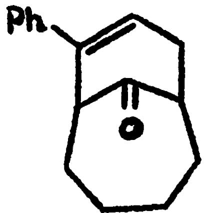

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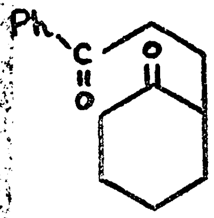

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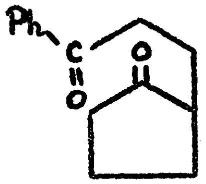

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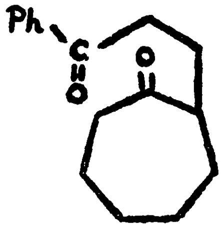

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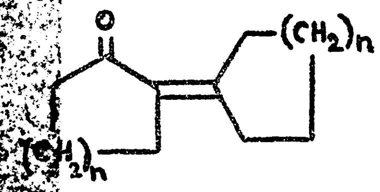

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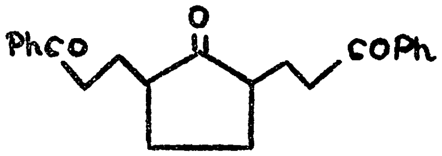

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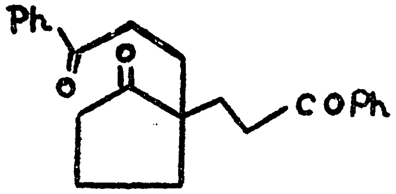

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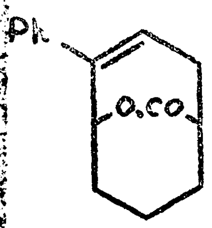

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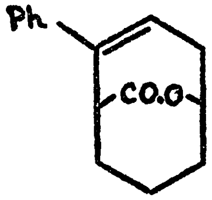

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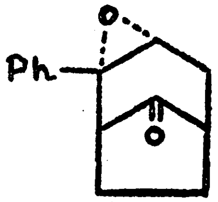

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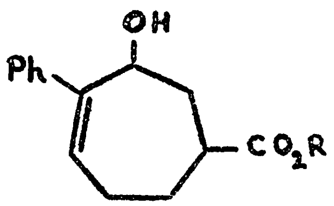

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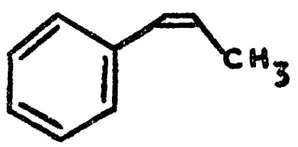

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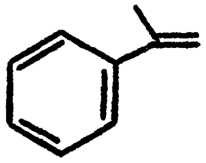

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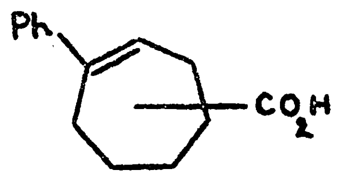

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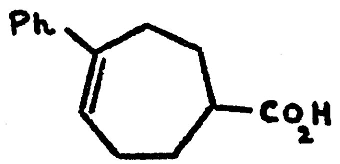

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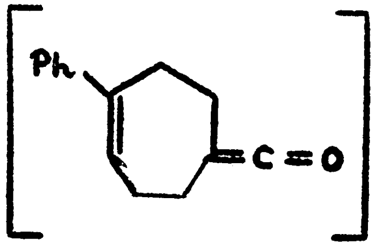

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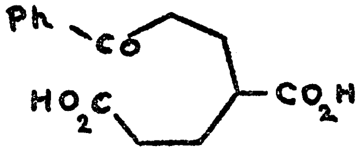

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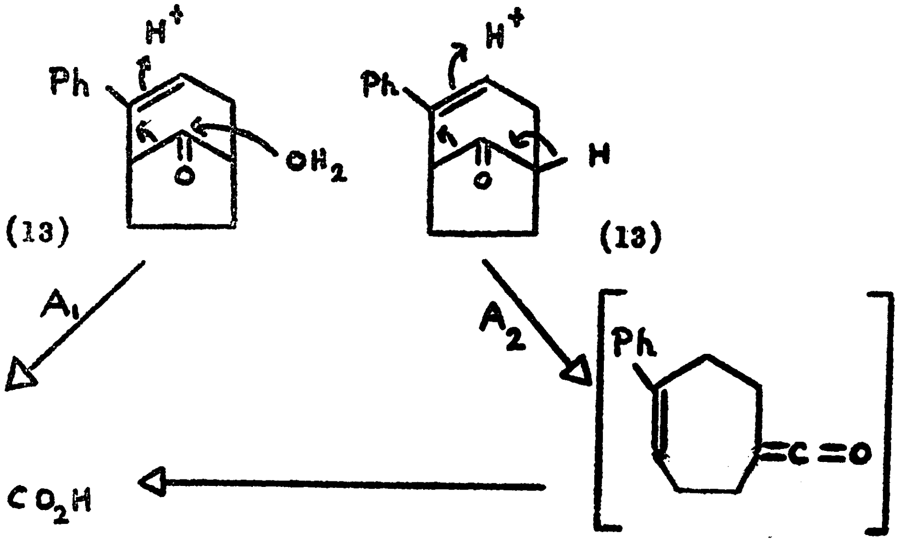

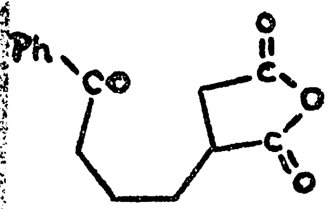

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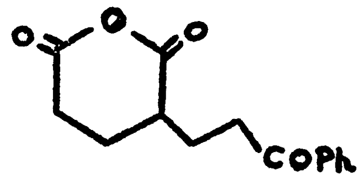

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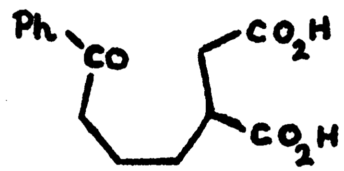

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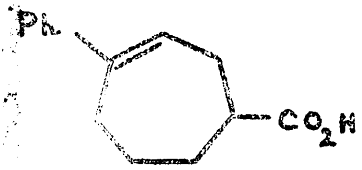

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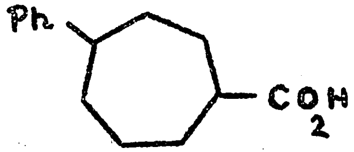

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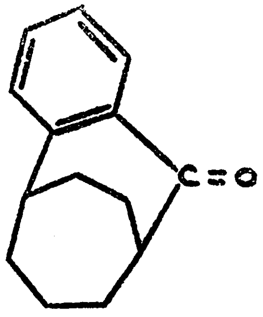

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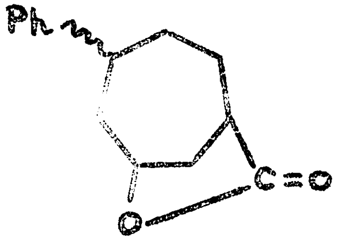

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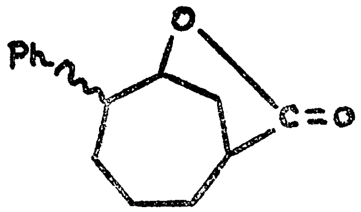

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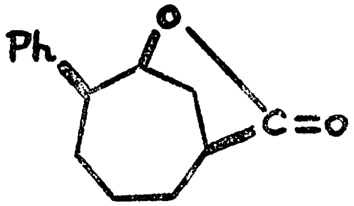

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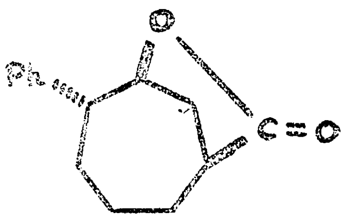

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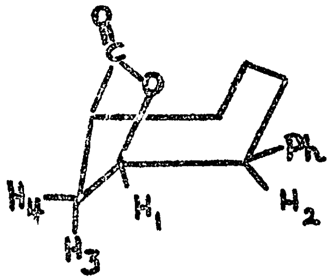

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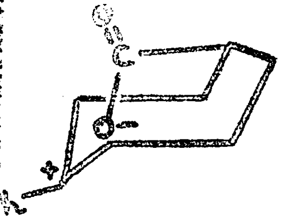

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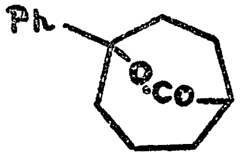

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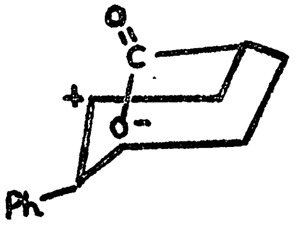

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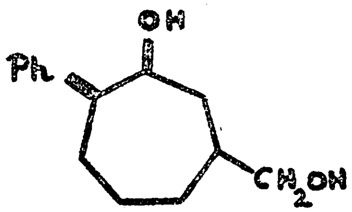

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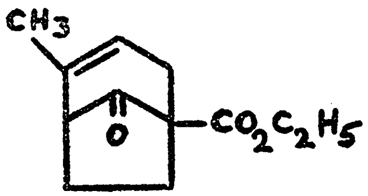

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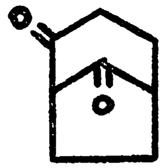

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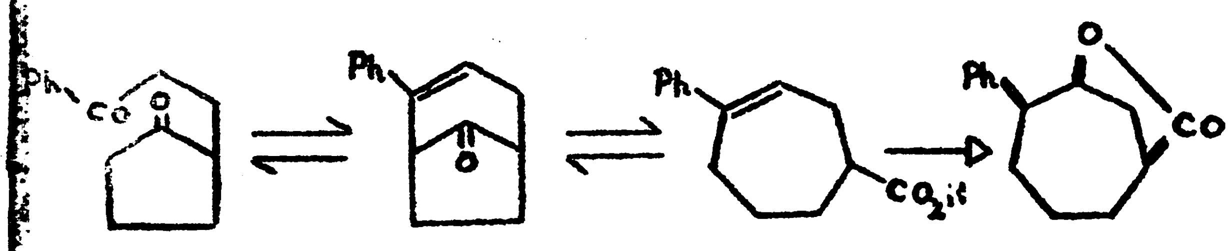

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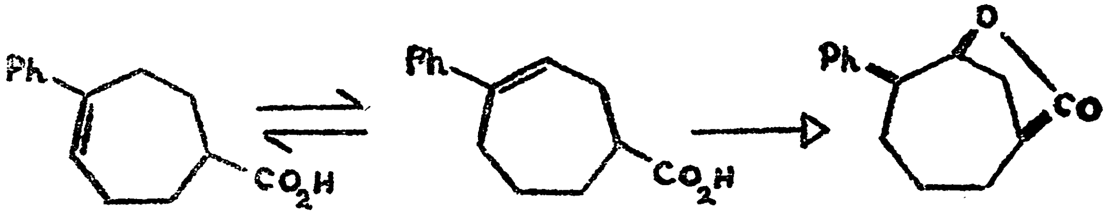

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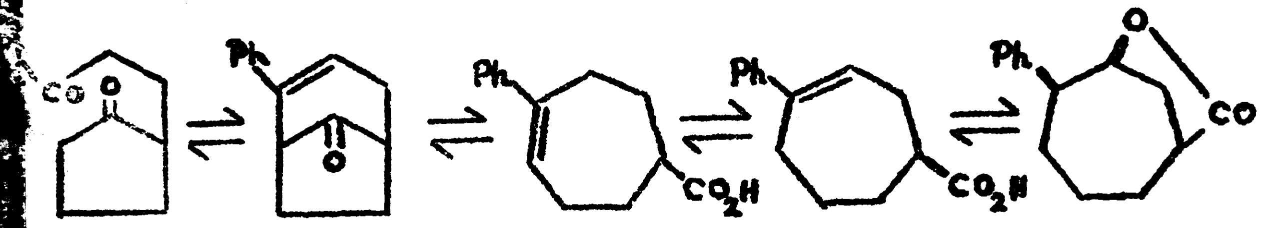

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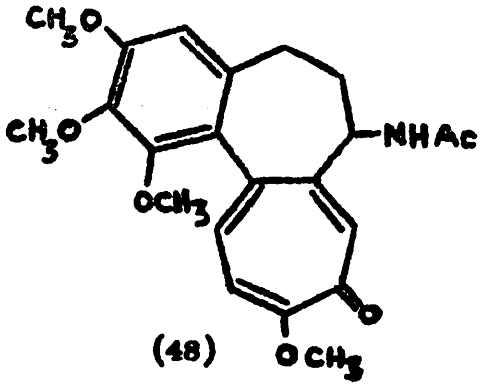

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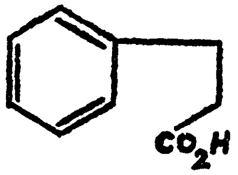

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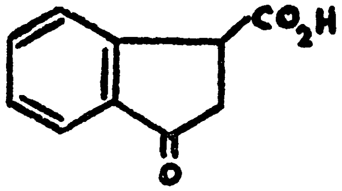

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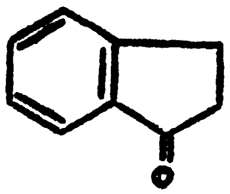

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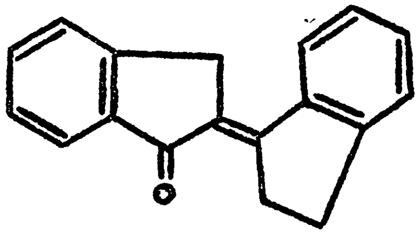

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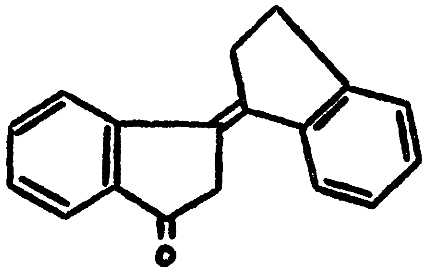

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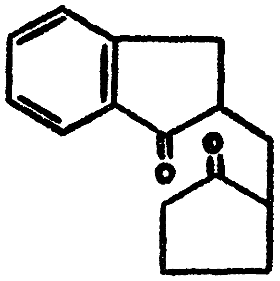

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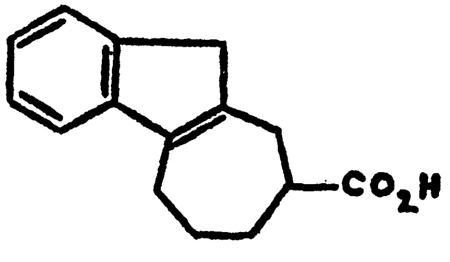

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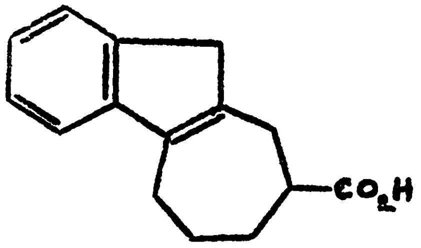

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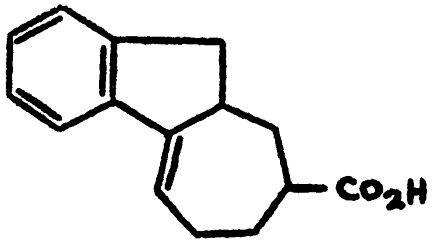

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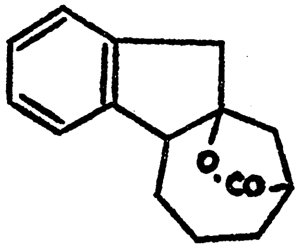

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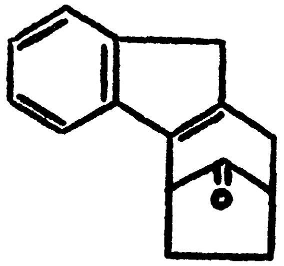

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