TROPOLONES

Thesis submitted

by

James K. Sutherland

for the degree

of

Doctor of Philosophy

of the

University of Glasgow.

Chemistry Department April, 1957

ProQuest LLC.
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106 – 1346

Acknowledgments

This work was carried out from 1954 to 1957 during the tenure of a D.S.I.R. Maintenance Allowance and under the direction of Dr. G.L. Buchanan to whom I express my deepest gratitude for constant encouragement and help. Thanks are also due to Dr. J.D. Loudon for stimulating discussion and advice.

Microanalyses were by Mr. Cameron, Miss Christie, and Miss Watt.

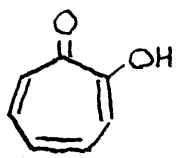
Contents

Contents (contd.)

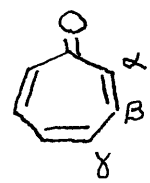
Part I

Some 7-Hydroxycycloheptatriene-3-ones and their 2:3-Dihydro-2:3-Methylenenaptha-1:4-quinone Isomers

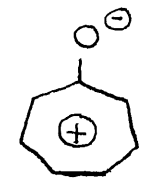
Since it is now firmly established that tropolone (I) and its derivatives behave as aromatic compounds[1], interest in this field has now centered on the parent tropone (II) and tropones hydroxylated in the β and γ positions i.e. the isotropolones.



I



II



III

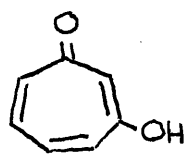
This stems from the suggestions of Buchanan[2] and of Doering and Knox[3] that tropone is the parent compound of the series and that it should be represented as cycloheptatrienylium oxide (III).

If these views are correct then tropone should behave as an aromatic compound and the shift of the hydroxyl group of tropolone to the β or γ position

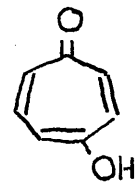
should not affect the aromatic properties of the molecule, though one would expect major differences in both physical and chemical properties between, on the one hand, the strongly intramolecularily hydrogen bonded tropolone, and, on the other, the two isotropolones (IV and V) where intramolecular hydrogen bonding is impossible.

So far no extensive investigations of the properties of any isotropolones have been reported; indeed, it is only recently that the syntheses of 3-[4] (IV) and 4-hydroxytropone (V)[5,6] have been described.

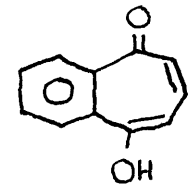
We decided to investigate this problem by examining the properties of a benzisotropolone (VI)[7], and, concurrently, to interest ourselves in the



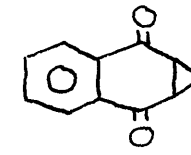
IV



V



VI



VII

chemistry of an isomeric compound which had been prepared at the same time and to which structure (VII) had been assigned.

Some 7-Hydroxybenzocycloheptatriene-7-one Derivatives (Sheet I) P 8a

The isotropolone (VI) was first prepared[7] from benzocycloheptene-3:7-dione (VIII) by the latter's conversion to the bis-enol acetate (IX) which reacted with N-bromsuccinimide to yield the isotropolone acetate (X), presumably by allylic bromination followed by spontaneous elimination of acetyl bromide. The acetate (X) was extremely labile and gave the isotropolone (VI) on shaking with cold sodium hydroxide solution.

The properties of the isotropolone were consistent with its structure (VI) - it was soluble in sodium hydroxide solution, gave a mono-2:4-dinitrophenylhydrazone and a mono-methyl ether, and upon catalytic hydrogenation yielded the diol (XI).

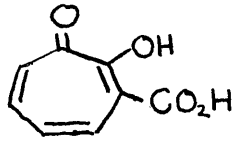
However in the above route the preparation of the bis-enol acetate (IX) was tedious requiring long periods of reflux and recycling with isopropenyl acetate before conversion of the dione (VIII) was complete. This difficulty was overcome by using the ester (XII; R = H) as starting material.

Measurement of the ultra violet spectrum of

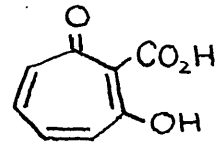
the latter (XII; R = H) showed that it had not the characteristic curve of the benzo<u>cyclo</u>heptene-3:7-dione system (see Table II, p 31a), the peaks being displaced to a longer wavelength, and examination of its infra red spectrum indicated the presence of strongly hydrogen bonded hydroxyl groups and little or no ketone carbonyl absorption. Thus it is more accurate to represent (XII; R = H) as the dienol and it is not surprising that the <u>bis</u>-enol acetate (XII; R = Ac) is formed in excellent yield under mild conditions (acetyl chloride and pyridine). The latter was converted, as before, with N-bromsuccinimide into the <u>iso</u>tropolone acetate (XIII; R = Ac) which with cold dilute alkali yielded an extremely insoluble sodium salt of the diester (XIII; R = Na). Acidification of this salt with concentrated hydrochloric acid (dilute had no effect) yielded the diester <u>iso</u>tropolone (XIII; R = H). More vigorous alkaline hydrolysis of the sodium salt gave, after acidification, the <u>iso</u>tropolone (VI) and carbon dioxide.

The ready decarboxylation of the intermediate acid in acid solution is probably due to the carboxyl groups being positioned β to a carbonyl or potential carbonyl group. However this ease

of decarboxylation is not apparent in the monocyclic series e.g. both 3-carbethoxy tropolone (XIV)[8] and 2-carbethoxy-3-hydroxytropone[9] (XV) are thermally



XIV



XV

stable and the former is decarboxylated only in refluxing aniline.

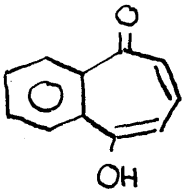
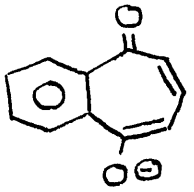
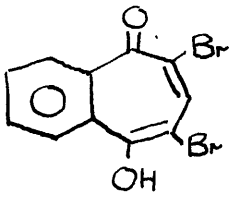
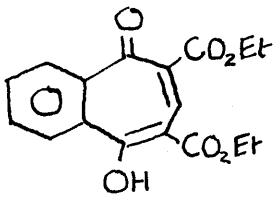
There is an interesting contrast in physical properties between the isotropolone (VI) and its dicarboxylic ester (XIII; R = H). The former has a high melting point, low solubility in organic solvents, and is deep yellow in color whereas the latter has a low melting point, is very soluble in organic solvents, and is almost colorless. The differences are again evident in their respective infra red spectra - (VI) in the solid state has a broad hydrogen bonded hydroxyl band from 3300 $cm.^{-1}$ to 2000 $cm.^{-1}$ and a strongly hydrogen bonded carbonyl

peak at 1470 $cm.^{-1}$, whereas the ester (XIII; R = H) shows a sharp hydrogen bonded hydroxy band at 2950 $cm.^{-1}$ and a ketone carbonyl at 1650 $cm.^{-1}$. These divergencies may be rationalised by accepting that in the isotropolone (VI) strong intermolecular hydrogen bonding is present whereas in the ester (XIII; R = H) there is intramolecular hydrogen bonding between the hydroxyl and carboxyethyl groups.

During the characterisation of the isotropolone (VI) it was noted that the ultra violet spectrum previously reported[7] for the latter was, in fact, that of its anion. Comparison of the spectra obtained in acid and alkaline solution (see Table I P 6a) show that, as is typical with tropolones, the short wavelength peak is not displaced in the anion whereas the long wavelength peaks are displaced bathochromically and are intensified.

Several reactions were carried out on the isotropolone (VI) e.g. nitration, reaction with thionyl chloride and p-toluenesulphonyl chloride, but in almost every case the results were indeterminate owing to the difficulty of purifying the products. Usually, owing to their insolubility, high vacuum sublimation was the only method available.

TABLE I

	λ_{max}^{EtOH} (log ε)
	231(4.47), 376(3.92).
	234(4.47), 370(3.83), 440(4.04).
	236(4.32), 266(4.18), 330(3.86), 390(3.76).
	241(4.45), 336(4.11).

However, the isotropolone (VI) reacted smoothly with two moles of bromine in acetic acid to yield a dibromide whose analysis, ultra violet and infra red spectrum indicated that it contained an isotropolone nucleus, but there were no indications whether this was a direct aromatic substitution or an addition followed by elimination of hydrogen bromide. Oxidation of the dibromide to phthalic acid with dilute nitric acid showed that there were only three positions in which the two bromine atoms could be placed.

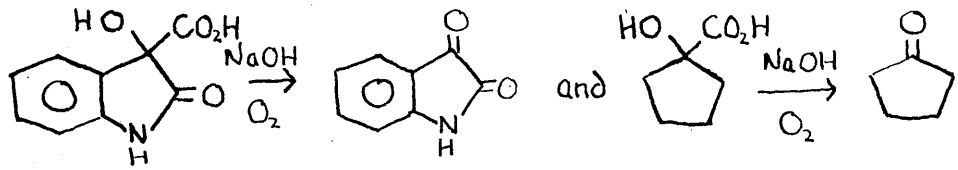
When bromination was carried out using one mole no monobromide could be isolated, a mixture of dibromide and starting material being indicated by the infra red spectrum.

From other observations (see later) we believed that a dibromide of structure (XVI) would rearrange with alkali to 2-hydroxynaphtha-1:4-quinone (XVII) and, on heating with 5N sodium hydroxide, or, in better yield, by fusion with potassium hydroxide, a small yield of the quinone was formed.

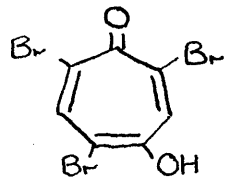
We prefer the mechanism shown (Sheet I) to any of the usual paths postulated for conversion of tropolones and their derivatives to benzenoid compounds[10] for two reasons - firstly, the latter rearrangements

invariably yield carboxylic acids, and, secondly, hydroxy and halotropones are difficult or even impossible to rearrange.

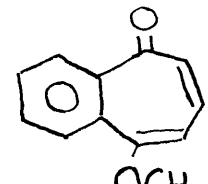
With regard to our mechanism, the first stage is unexceptional, merely an hydrolysis of bromine to hydroxyl. The next reaction is oxidation to the "tropoloquinone" (XVIII) which could occur by the usual two stage radical mechanism for the oxidation of quinols to quinones in alkaline solution, oxygen being the electron acceptor. A benzilic acid rearrangement would now yield (XIX) which by oxidative decarboxylation would give the quinone (XVII). For the latter reaction there are numerous analogies e.g.



The above orientation of the bromine atoms is also indicated by the demonstration that 4-hydroxy tropone upon bromination yields the tribromide (XX)[6].

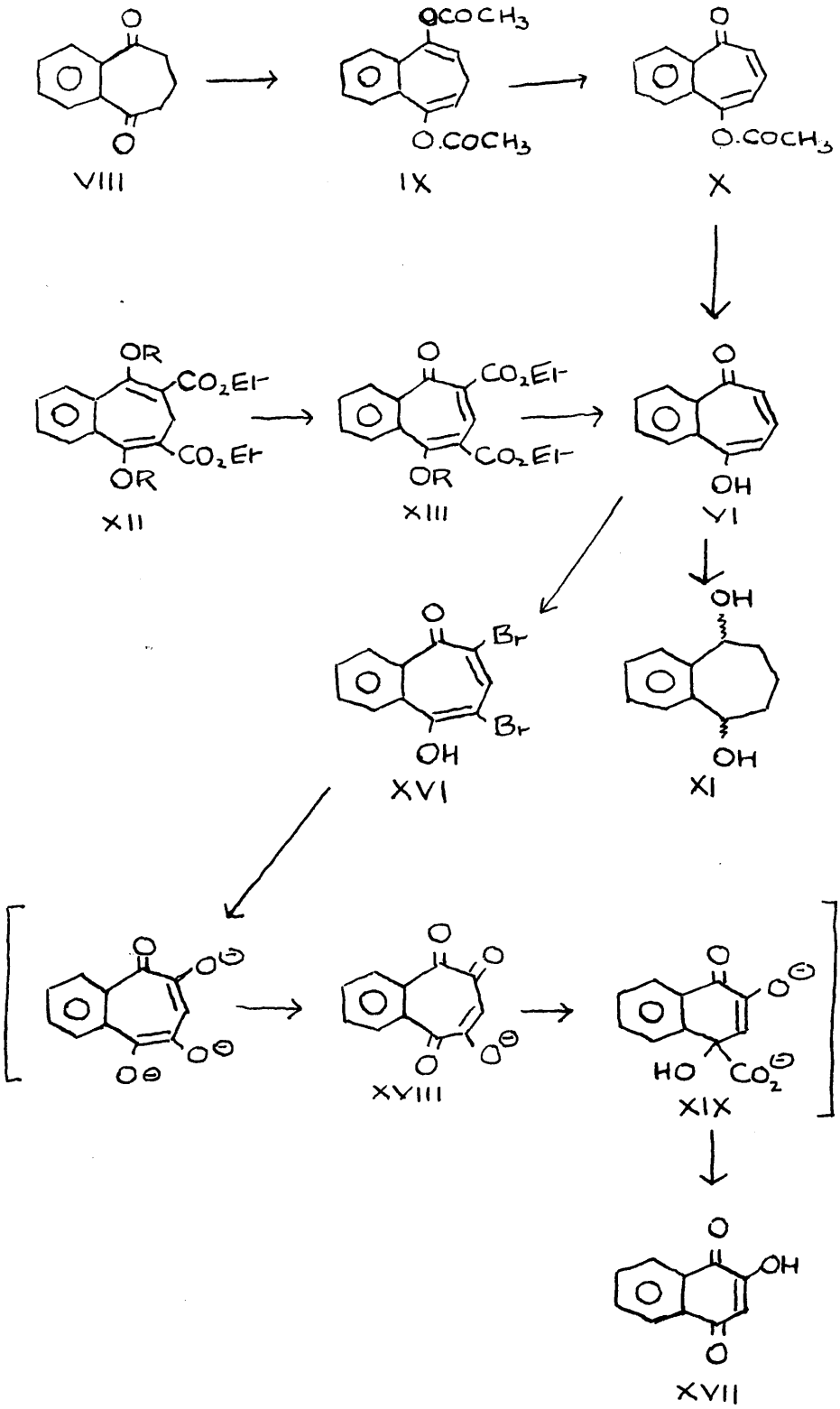


XX



XXI

SHEET I


VIII
IX
X
XII
XIII
VI
XVI
XI
XVIII
XIX
XVII

Hydrolysis of the dibromide (XVI) to the dihydroxy compound was also attempted using aqueous ammonium chloride and sodium acetate solution. Color tests and melting points on the products indicated that rearrangement to the quinone had occurred but insufficient amounts were available for characterisation. Sodium ethoxide in ethanol and 5N hydrochloric acid, under the conditions tried, appeared to leave the molecule unaffected.

There was one negative result of note - the isotropolone (VI) was found to be stable to alkaline hydrogen peroxide unlike tropolone or αβ-unsaturated ketones in general.

Syntheses of 2:3-Dihydro-2:3-methylenenaphtha-1:4-quinone Derivatives (Sheet II P18a)

Our interest in the supposed cyclopropane dione (VII) was twofold - firstly, it had been produced on pyrolysis of the isotropolone methyl ether[7] (XXI) in a rearrangement of sufficient novelty to make a determination of the structure of the product desirable; secondly, the properties of compounds of the above structure are interesting per se since they are cyclopropane anologues of

naphtha-1:4-quinones and it would be of interest to compare the conjugative capacity of the cyclopropane ring with that of the double bond. In recent years there has appeared evidence[11] (mainly spectroscopic) that the δ electrons of the cyclopropane ring can interact with the p and π electrons of various unsaturated groupings e.g. the carbonyl.

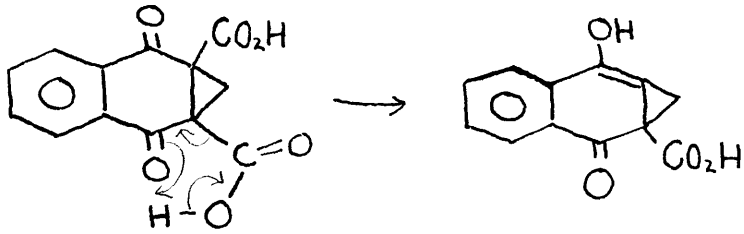
The compound (VII) was originally prepared[7] by treatment of the dione (VIII) with one mole of N-bromsuccinimide followed by dehydrobromination of the monobromide with 30% aqueous trimethylamine. It was insoluble in alkali, stable to aqueous potassium permangamate, and gave a bis-2:4-dinitrophenyl-hydrazone - all inconsistent with its formulation as the benzisotropolone (VI) which was prepared at a later date. The most reasonable rationalisation of these properties was that 1:3 dehydrobromination had occurred especially as analogous cases were known[12] where the preferential removal of an active hydrogen from the 3 position, rather than the inactive 2, took place.

The first synthetic proof of structure attempted in this work started from the di-β-ketoester (XII; R = H) which readily reacted with one mole

of N-bromsuccinimide to give the bromoester (XXII). The latter readily dehydrobrominated with 30% aqueous trimethylamine or 5N sodium hydroxide yielding the ester (XXIII).

It was then envisaged that this ester would on "ketonic" hydrolysis yield the dione (VII) and under conditions of "acidic" hydrolysis give a mixture of phthalic and cyclopropane dicarboxylic acids; this constituting a complete proof of structure of both the ester (XXIII) and the dione (VII). In fact we were unable to carry through either of the reactions.

Hydrolysis of the ester (XXIII) with dilute acid yielded only the products of a deep seated decomposition, containing a small quantity of a purple compound (probably a semiquinone). Mild hydrolysis with hot alkali gave the dicarboxylic acid (XXIV) in excellent yield but all attempts to decarboxylate it were fruitless, leading to return of starting material or extensive decomposition. A possible explanation of the absence, in this case, of the smooth decarboxylation usually associated with β-ketoacids is evident if the mechanism of decarboxylation is considered (see XXIV). From the arrows one sees that the kinetic product of decarboxylation will be the enol (XXV)

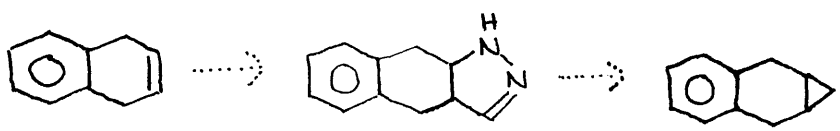


XXIV XXV

which would be highly strained, in fact so highly strained that alternative paths of reaction occur before there is sufficient energy for enol formation. Indeed, there is no evidence for enolisation of the dione (VII) from its infra red spectrum in solution in contra-distinction to the dione (VIII).

Hydrolysis of the ester (XXIII) with concentrated methanolic potassium hydroxide yielded a mixture from which only phthalic acid could be isolated in a pure state.

Another abortive attempt to synthesise the dione (VII) was based on the well known reaction of diazomethane with double bonds to form pyrazolines which can be pyrolysed to yield cyclopropanes. 1:4-Dihydronaphthalene (XXVI) was set aside with

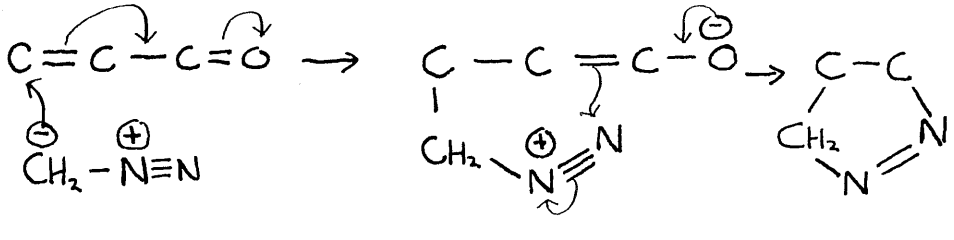


XXVI XXVII XXVIII

diazomethane in ether in the hope that the pyrazoline (XXVII) would be formed and could be pyrolysed to the hydrocarbon (XXVIII), but only naphthalene could be isolated from the reaction mixture and in yield insufficient to indicate whether it was formed by disproportionation of the starting material or by an oxidising reaction of the diazomethane.

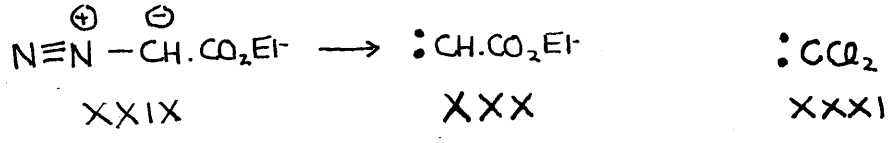
Our attention then turned to a route related to the latter unsuccessful one viz. the addition of diazo acetic ester to an olefinic double bond. It appears that diazomethane adds slowly, if at all, to isolated olefinic bonds whereas it reacts readily with double bonds conjugated to an unsaturated grouping. Diazoacetic ester reacts readily with either. This differing reactivity may be explicable on a mechanistic basis.

Diazomethane is a nucleophilic reagent and should react more readily with a conjugated double bond e.g. an αβ-unsaturated ketone, which is electrophilic, than with an olefinic double bond which is



nucleophilic.

Unlike the diazomethane addition that of diazoacetic ester appears to involve radical intermediates rather than ionic and would thus differ much less in its action to conjugated and isolated double bonds. It is postulated that the diazoacetic ester (XXIX) is decomposed on the copper bronze catalyst to the diradical (XXX) which reacts with



XXIX XXX XXXI

the double bond. This path is supported by the formation of diethyl fumarate during reaction by dimensation of the diradical (XXX) and by the fact that pyrazolines have not been isolated from reactions of diazoacetic ester with double bonds under the usual conditions.

In support of the ionic mechanism for diazomethane reactions it has been shown that the dichlorocarbene diradical (XXXI) unlike diazomethane adds readily to isolated olefinic linkages[13].

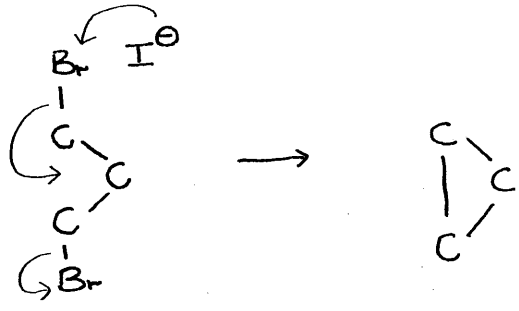
To return to our synthesis. Reaction of allyl benzene (XXXII) at the boiling point with diazoacetic ester in the presence of copper bronze yielded the

mixture of esters (XXXIII) which was hydrolysed to the mixture of acids (XXXIV) from which two anilides were prepared in a ratio of approximately ten parts of low melting to one part of high melting. Fortunately the most abundant isomer was the cis- acid which is the only one which it is sterically possible to cyclise to the tetralone (XXXV) and the recovery from the cyclisation mixture of only the acid which gave the high melting anilide proved that it had the trans configuration. The cyclisation can be effected by polyphosphoric acid or, better, by the action of aluminium chloride on the chlorides of the acids (XXXIV) in cold ethylene dichloride. The tetralone was characterised by the preparation of a 2:4-dinitrophenyl hydrazone and by its infra red spectrum (ν_{max} 1675cm^{-1}).

There remained only the oxidation of the methylene group to a carbonyl to complete the synthesis of the dione (VII) and this was achieved with chromium trioxide in boiling acetic acid after some indeterminate results with selenium dioxide.

A third synthesis of the dione (VII) started from the dione (VIII) which was reacted with two moles of bromine to yield the dibromodione (XXXVI) which

yielded the dione (VII) on treatment with sodium iodide in acetone. This modification of the Finkelstein reaction had already been used in the synthesis of cyclopropanes from certain active 1:3-dibromo compounds[14] and undoubtedly proceeds by the mechanism shown. The ease with which it



occurs in the above case is no doubt due to the close proximity in the bromo compound of the two carbon atoms which are to be coupled.

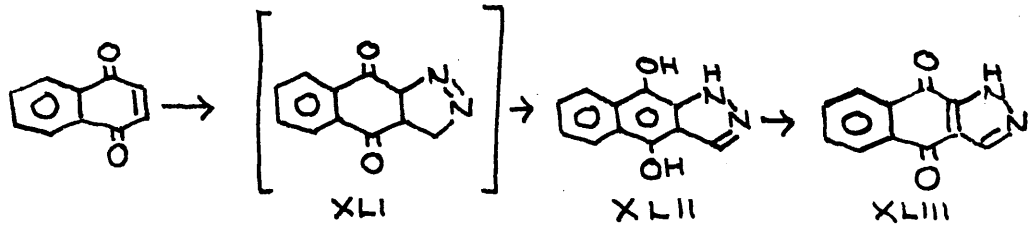
Reaction of the dibromodione (XXXVI) with aqueous trimethylamine or 5N sodium hydroxide leads, as in the original example to 1:3 elimination of hydrogen bromide yielding a bridge head substituted bromodione (XXXVII),.

Mono- ~~and~~ or dibromination of the dione (VIII) was completed almost instantaneously at room temperature but preparation of the tribromodione

(XXXVIII) was more difficult but could be achieved by long standing or refluxing with three moles of bromine. In this case also aqueous trimethylamine caused 1:3 elimination of hydrogen bromide yielding the dibromodione (XXXIX) but with 5N sodium hydroxide the only product which could be isolated was 2-hydroxynaphtha-1:4-quinone (XVII). Here 1:2 elimination of hydrogen bromide probably takes place giving the dibromoisotropolone (XVI) which rearranges by the mechanism discussed before. That the precursor of the quinone (XVII) is the dibromocyclopropane (XXXIX) is excluded by its stability under the conditions of rearrangement. Also unexpectedly the modified Finkelstein reaction on the tribromide (XXXVIII) did not yield the monobromide (XXXVII) but a mixture which we were unable to separate.

The tetrabromide (XL) yielded the dibromide (XXXIX) with sodium iodide in acetone or with aqueous trimethylamine. The latter debromination with reagents usually associated with dehydrobromination has been noted before[15], but in this case it cannot be precluded that the small yield of dibromide arose from some tribromodione (XXXVIII) present in the crude tetrabromination mixture.

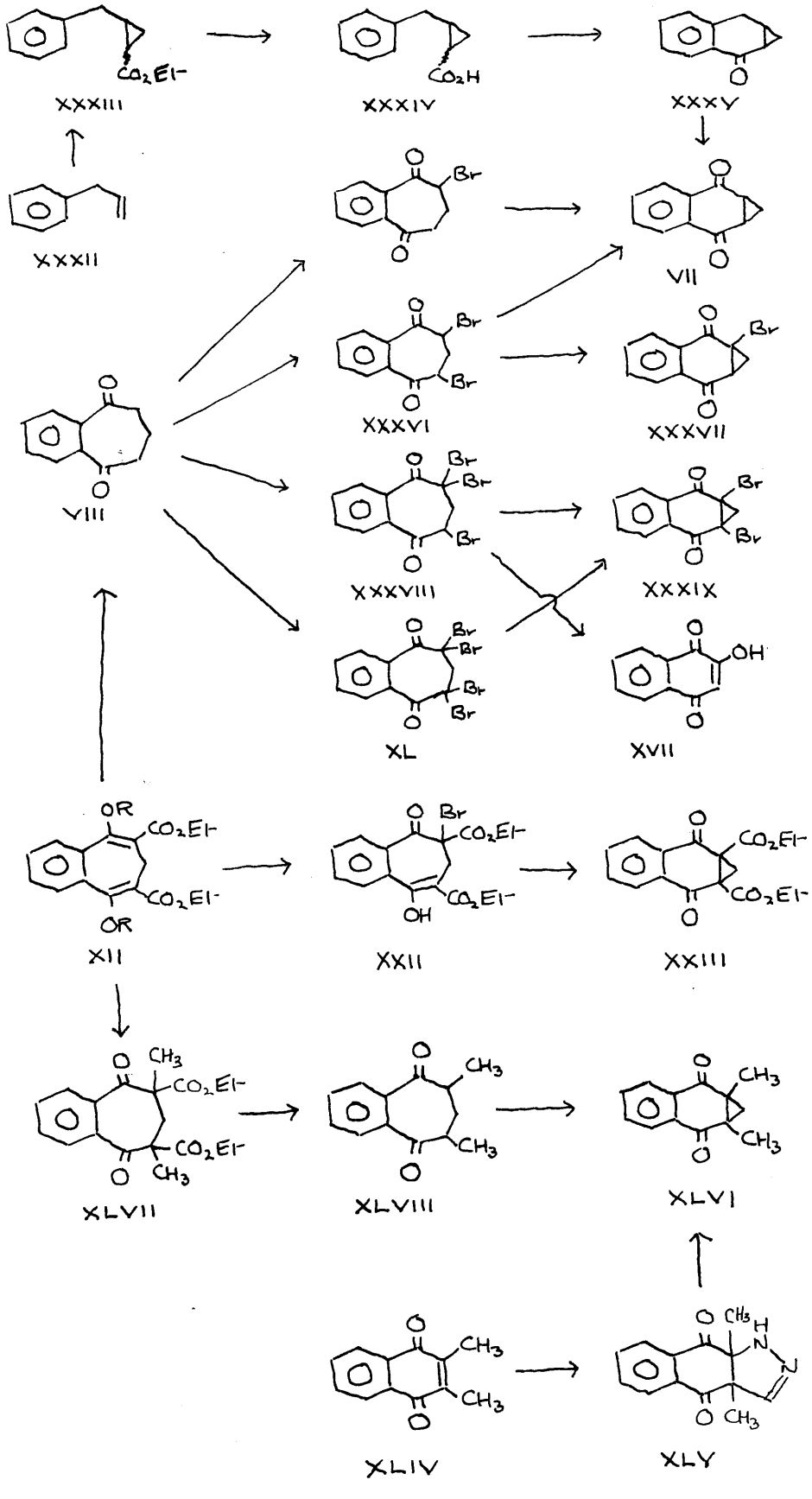
From our previous observations on the mode of action of diazomethane, naphtha-1:4-quinone should provide an obvious starting material for the synthesis of the dione (VII) since reaction with diazomethane followed by pyrolysis should yield the ketone (VII). However this reaction has been carried out[16]. The addition occurs as expected but the primary adduct



(XLI) immediately tautomerises to the quinol (XLII) which even on crystallisation is oxidized to the quinone (XLIII).

We therefore determined to use a quinone in which enolisation of the primary adduct could not occur and, accordingly, reacted 2:3-dimethylnaphtha-1:4-quinone (XLIV) with diazomethane and pyrolysed the intermediate pyrazoline (XLV) to the dimethyldione (XLVI). This structure was confirmed by its synthesis from the ester (XII; R = H) which was methylated with methyl iodide and sodium ethoxide to yield (XLVII). This

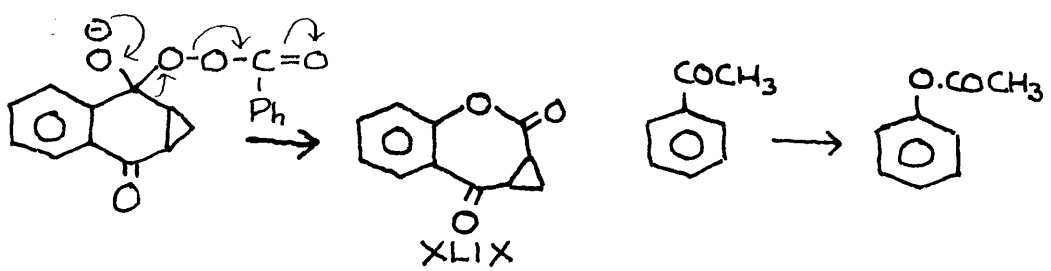
SHEET II


XXXIII
XXXIV
XXXV
XXXII
VII
VIII
XXXVI
XXXVII
XXXVIII
XXXIX
XL
XVII
XII
XXII
XXIII
XLVII
XLVIII
XLVI
XLIV
XLV

ester proved extremely resistant to hydrolysis (probably due to the carboxyethyl groups being a trisubstituted) but under forcing conditions yielded the dione (XLVIII) which by the bromine-sodium iodide-acetone reactions yielded the dione (XLVI) identical with that previously obtained.

Properties of 2:3-Dihydro-2:3-methylenenaphtha-1:4-quinone and its Derivatives (P23a)

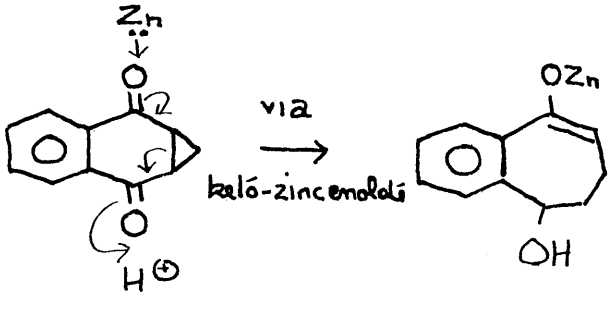
One of the most notable characteristics of this ring system is its great stability to oxidising agents - the dione (VII) was recovered unchanged from boiling chromium trioxide in acetic acid, boiling dilute nitric acid, and several hours at 100° with alkaline potassium permanganate. The stability is undoubtedly due to it being composed of two groupings traditionally stable to oxidation viz. a negatively substituted benzene ring and a like substituted cyclopropane group. The dione (VII) was also stable to perbenzoic acid in chloroform, none of the desired oxidation to the lactone (XLIX) taking place, cf acetophenone.



The compounds of this series were sensitive to mineral acids yielding purple tars which probably contained quinonoid materials but they were not investigated.

During the preparation of carbonyl derivatives of various compounds it was noted that they were subject to steric hinderance with regard to oxime formation under standard conditions e.g. the dione (VII) gave a bis-oxime, the bromodione (XXXVII) a mono oxime, and no oximes could be prepared from compounds with two substituents at the bridgehead. The dimethyl dione (XLVI) surprisingly gave a mono-2:4-dinitrophenyl hydrazone with 2:4-dinitrophenylhydrazine hydrochloride in methanol, formation of the bis compound being excluded by the extreme insolubility of the mono compound. Apparently there are different steric requirements for oxime and 2:4-dinitrophenylhydrazone formation under the standard conditions. Attempts to effect Beckman rearrangement of the bis-oxime of the dione (VII) with polyphosphosphoric acid returned starting material a small amount of the parent dione (VII) presumably from the oxime by hydrolysis with the acid. It is perhaps not surprising that this reaction did not go as the aryl migration would involve considerable steric strain.

The reduction of compounds of this group was studied fairly extensively (see Sheet P23a III). The most effective reducing agent was zinc dust in boiling acetic acid which converted the dione (VII), the monobromodione (XXXVII), and the dibromodione (XXXIX) to the ketol (L) characterised by its infra red spectrum (ν_{max} 3410,1675cm^{-1}), its 2:4-dinitrophenylhydrazone (ν_{max}3485cm^{-1}), its oxime, and its oxidation to the dione (VIII) by chromium trioxide in cold acetic acid. An alternative formulation of the ketol (LI) was eliminated by a Rast molecular weight determination; also it is unlikely that a pinacol reduction would be effected by Adam's platinum oxide in ethanol which also reduced the dione (VII) to the ketol (L). That this type of selective reduction is not due to the cyclopropane ring being present and proceeding by the mechanism shown to



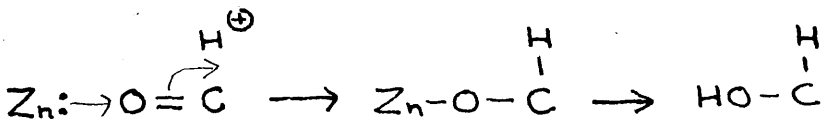
give a zinc enolate stable to further reduction, is demonstrated by the reduction of the dione (VIII) to the ketol (L) with the same reagent.

In the compounds where the bridgehead positions α to the carbonyl groups are substituted, reduction stops at the dione stage and no ketol is formed. Thus the diester (XXIII) was reduced to (XII; R = H) and the dione (XLVIII) was obtained from (XLVI). Here, as in the preparation of carbonyl derivatives, a steric effect is operative.

A possible explanation of the reduction stopping at the ketol stage is apparent when one considers the electromeric effects of the carbonyl groups. A single carbonyl adjacent to an aromatic ring will withdraw electrons mainly from the ortho and para positions at the same time making the carbonyl less reactive to nucleophilic reagents due to partial saturation of the positive dipole on the carbonyl carbon atom. When another carbonyl group is placed ortho (or para) to the original one then the ortho carbon atom bearing the carbonyl group will have a reduced electron density i.e. the two carbonyl groups are electronically in opposition and the result of this will be that each carbonyl

carbon atom has a lower electron density than that in the acetophenone and is thus more reactive towards nucleophilic reagents and more highly polarised. This differing character of the carbonyl groups is borne out by the positions of carbonyl absorption in the benzocycloheptene-3:7-dione system (1695cm^{-1}) and and the acetophenone types (1675cm^{-1}).

The dione type of carbonyl group reacts with the zinc dust and acetic acid to give the ketol by the mechanism shown below but with the reduction of one

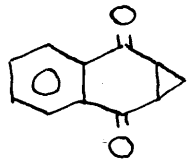


of the carbonyl groups the remaining one reverts to the less highly polarised acetophenone type which is stable to the reducing agent.

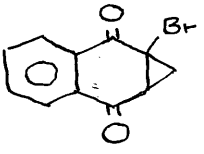
Our attempts to carry out a Wolff-Kishner reduction on the dione (VII) were uniformly unsuccessful leading to extensive decomposition or return of hydrazone.

The dione (VII) also proved stable to sodium in liquid ammonia and was recovered in about 80% yield from lithium in liquid ammonia and ethanol. In the latter case a small quantity of an amorphous, yellow, alkali soluble solid was also isolated but

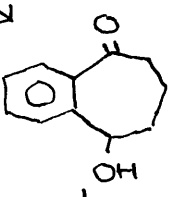
SHEET III



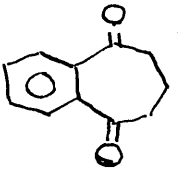
VII



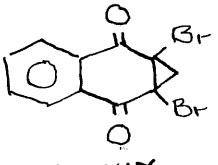
XXXVII



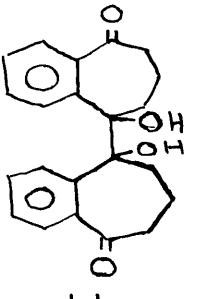
L



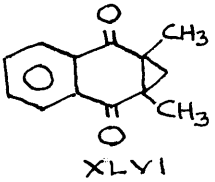
VIII



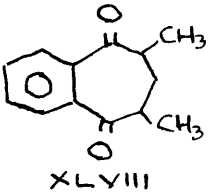
XXXIX



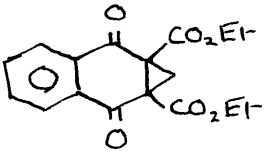
LI



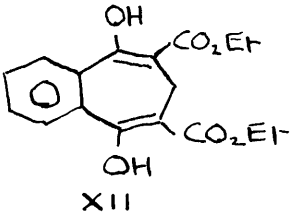
XLVI



XLVIII

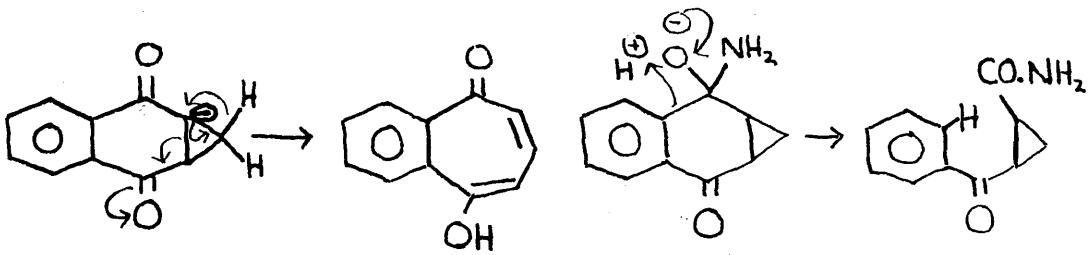


XXIII



XII

it could not be purified by vacuum sublimation and was of the same nature as that obtained from refluxing the dione (VII) in ethanol containing sodium ethoxide. The product hoped for was the



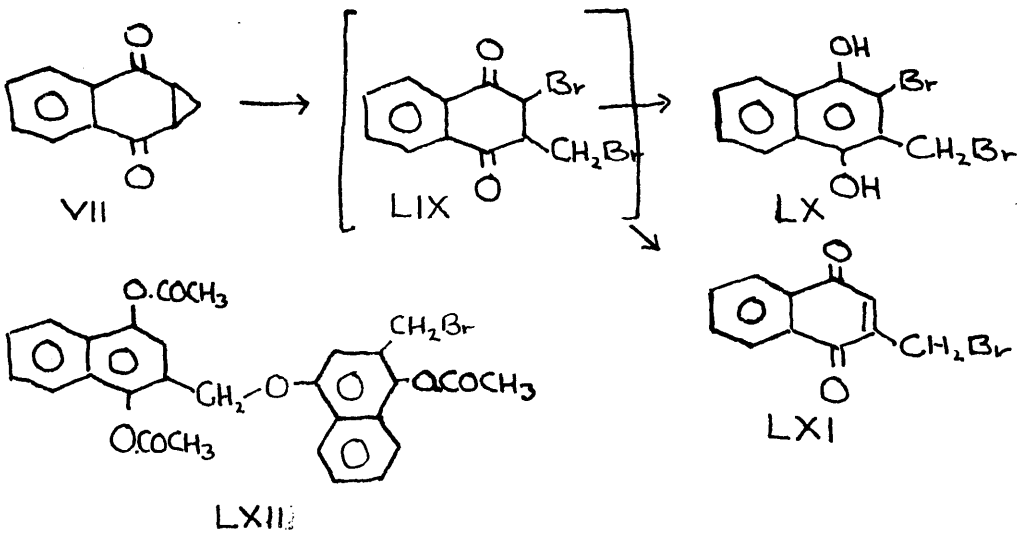
VII VI LII

benzo<u>iso</u>tropolone (VI) yielded by the mechanism shown above, however in no case could the pure <u>iso</u>tropolone be isolated but the sublimed material from one reaction had an ultra violet spectrum suggestive that such a rearrangement had occurred. Surprisingly the dione (VII) was also stable to sodium amide in liquid ammonia and refluxing xylene. One might have expected either the latter rearrangement to take place as above or scission of the molecule to the keto amide (LII).

It is now apposite to compare our work with some observations reported on similar compounds by Sorrie

and Thomson[15] (see P30a Sheet IV). In one paper[15a] they describe the synthesis of (LIII) and (LIV). The dibromide resulted from reaction of the dione (LV) with four moles of bromine and debromination of the resulting tetrabromide (LVI) with pyridine. The structure of the latter was established by its conversion with hydrogen bromide to the naphthazarin (LVII), by its reaction in aluminium chloride - sodium chloride melt to yield another naphthazarin (LVIII), and by its reduction with three moles of hydrogen to the parent dione (LV).

Our attempts at opening the cyclopropane ring with bromine and hydrogen chloride were conducted on the dione (VII). One mole of bromine yielded a violet solid (perhaps a semiquinone) after exposure of the reaction mixture to air suggesting that the



intermediate (LIX) had enolised to the dihydroquinone (LX) rather than eliminated hydrogen bromide to give the quinone (LXI), but attempts to oxidize the product were unsuccessful and reductive acetylation was not reproducible, but in one case a product was isolated which analysed for a compound of structure (LXII) and there were indications that the same compound was obtained from reductive acetylation of the quinone from (LX) but we were unable to purify the product sufficiently to establish this.

The action of hydrogen chloride on the dione (VII) also gave a violet solid which did not give well defined products on reductive acetylation.

In their paper[15a] Sorrie and Thomson note that the bromine atoms in the bridgehead substituted compounds (LIII and LIV) were stable to alkaline hydrolysis and displacement by cyanide. In this we concur and have shown that our analogous compounds are unchanged by refluxing 5N sodium hydroxide, ethanolic sodium acetate, aniline, and potassium iodide. This exceptional stability of bromines α to a carbonyl group is understandable in view of the Walden inversion required in an S_N2 substitution. In the above cases

inversion of the receptor carbon atom is impossible without rupture of the cyclopropane ring since it would give rise to the impossibly strained trans fusion of a six membered ring to a three membered one. Reaction by a S_N1 mechanism would give an α keto carbonium ion which would be difficult to form and would probably rearrange in this system.

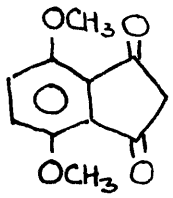
In another paper[15b] Sorm and Thomson describe some attempts to prepare the isotropolone (LXIII). From the dione (LV) they prepared first the mono- and then the bis-enolacetates (LXIV and LXV) both of which reacted with N-bromosuccinimide yielding the bromoacetate (LXVI) in poor yield. This compound was hydrolysed with potassium hydroxide to the isotropolone (LXIII) which was formulated as the diketo rather than the keto enol form because it reacted as a diketone and no alkyl or acyl derivatives could be prepared. That no extensive rearrangement had taken place was demonstrated by its hydrogenation to the parent dione (LV).

All the above evidence is compatible with its formulation as the cyclopropane compound (LXVII) but this was rejected on the basis of its solubility

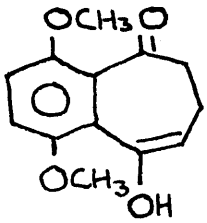
in hot sodium carbonate solution and warm dilute sodium hydroxide and its recovery therefrom on acidification.

We believe that the compound is correctly formulated as the cyclopropane (LXVII) and that the solubility in hot alkali is merely a physical solubility.

Our reasons for this view are as follows. Firstly the ultra violet spectrum of the compound is extremely similar to that of the two cyclopropane compounds (LIII and LIV) and that of (LXIII) is not likely to be so. Secondly the authors were able to prepare a trialkyl derivative (LXVIII) from the benzo derivative of (LXIII) but not from (LXIII) in which the carbonyl group would be expected to enolise into conjugation with the double bond as easily as does the carbonyl in (LXVIII) into conjugation with the benzene ring. Next Sorrie and Thomson ascribe the difficulty of enolisation of the carbonyl in (LXIII) to the presence of the methoxyls in the peri position quoting as an analogy the difficult enolisation of (LXIX). However we believe that consideration of the properties of the dione (LV) excludes this view.



LXIX

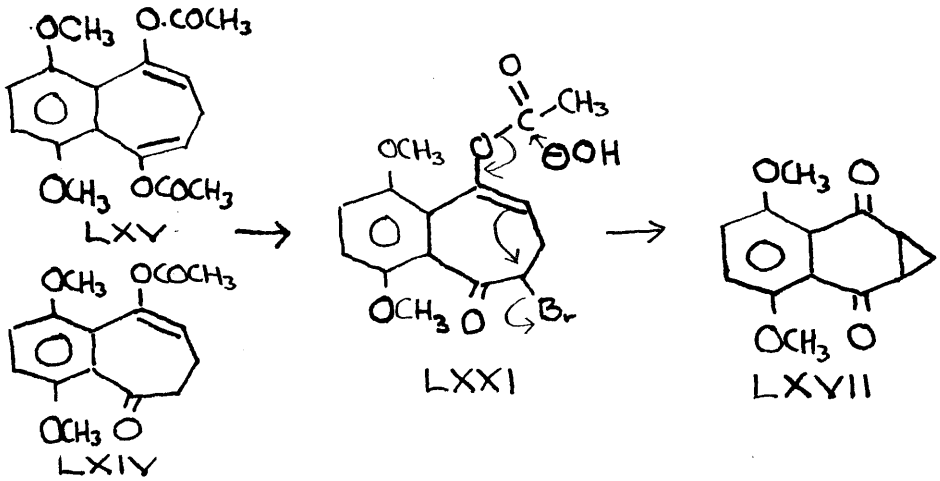


LXX

The dione (LV) gives under mild conditions and in good yield first a mono-enolacetate (LXIV) and then under more vigorous conditions a bis-enolacetate in contrast to the nonmethoxylated dione (VIII) which with difficulty gives a bis-enol acetate; no mono-enolacetate being isolated on working up the partially reacted material. The latter dione (VIII) also gives a bis-oxime in contrast to the mono-oxime prepared from (LV). Also the ultra violet spectrum of (LV) is anomalous since its long wavelength peak is displaced bathochromically about 45 mμ. in the cyclo-propane compounds (LIII and LIV). This was ascribed by Sorrie and Thomson to the conjugative effect of the cyclopropane ring but as is seen from our work (Table II) this displacement is only about 5 mμ. . We believe that the preceeding evidence indicates that the dione (LV) exists predominantly in the keto enol form (LXX).

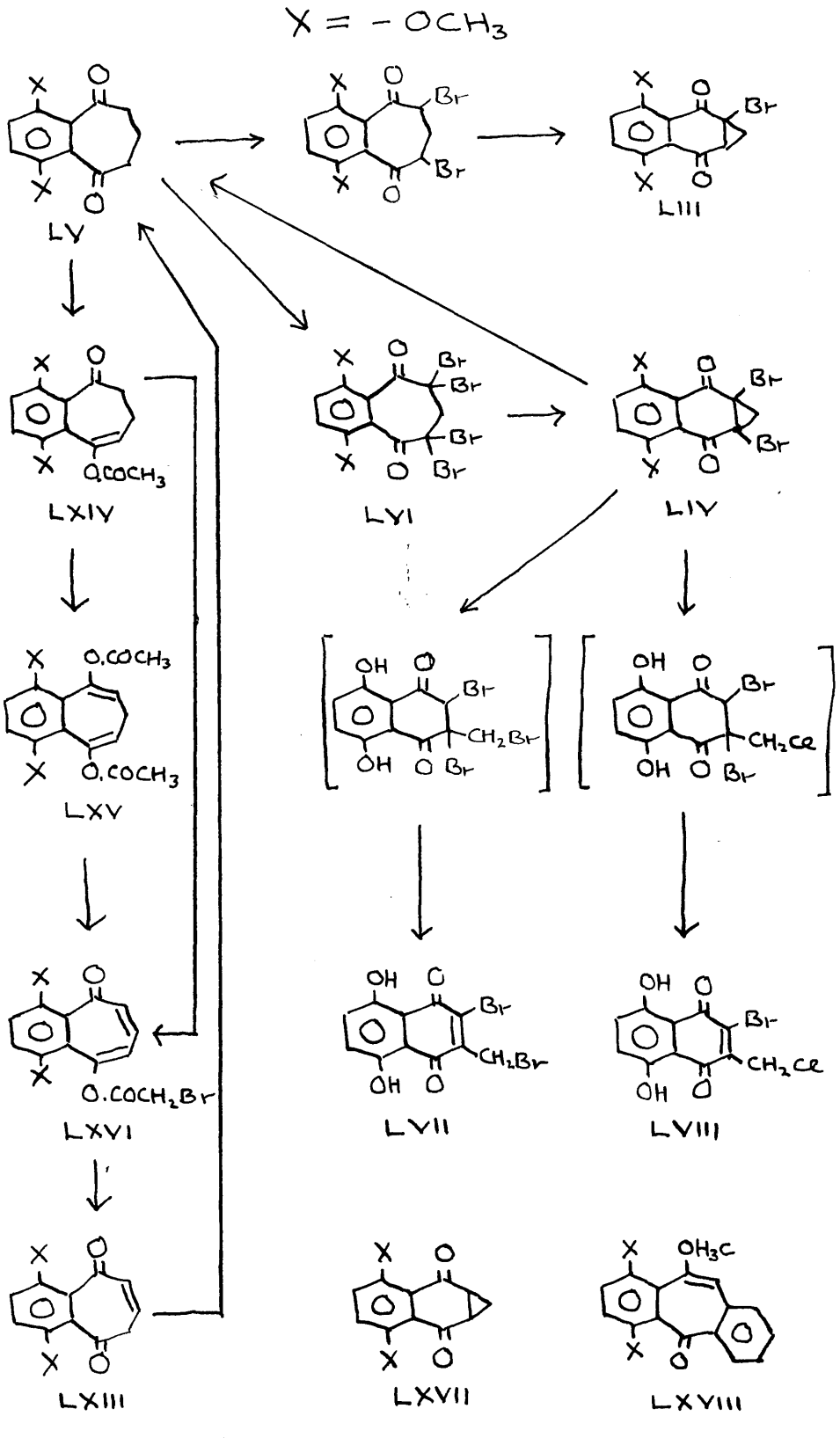
P31a

To account for the formation of the cyclo-propane compound (LXVII) we propose the following mechanism. Firstly the mesomeric effects



of the methoxy groups affect the allylic position in such a manner that the usual allylic bromination does not occur so that the mono-enolacetate (LXIV) yields the α-bromoketone (LXXI) which is also produced from the bis-enol acetate (LXV) in the manner of the invariable action of N-iodosuccinimide on enolacetates[17]. Indeed there are a few cases known where N-bromsuccinimide yields the α-bromoketone rather than the allylically substituted enol acetate[18]. This α-bromoketone (LXXI) is the compound formulated as the bromoacetate (LXVI) by Sorrie and Thomson. This with potassium hydroxide solution is hydrolysed to the dione (LXVII) by the mechanism shown; 1:2 elimination of hydrogen

SHEET IV


X = -OCH3
LV
LIII
LIV
LVI
LXIV
LXV
LXVI
LXIII
LVII
LVIII
LXVII
LXVIII

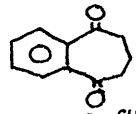
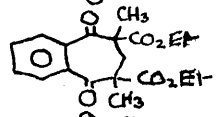
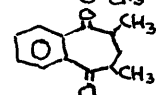
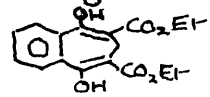
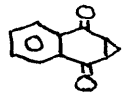
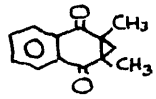
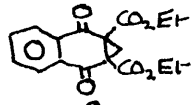
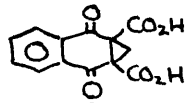
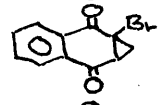
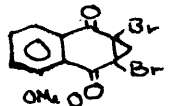
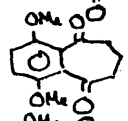
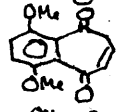
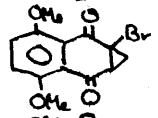
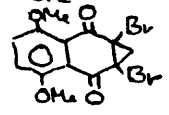
bromide being inhibited due to the difficulty of removing the allylic proton which is tightly bound because of the high electron density on the carbon atom of the double bond, relayed there by the mesomeric effect of the methoxyl group.

As mentioned before the ultra violet spectra of the benzocycloheptene-3:7-dione system is very similar to that of the compounds of the cyclopropane series, the bands in the latter being shifted about 5mμ. to the visible (see Table II, p 31a). This indicates that the δ-π interactions of the electrons of the cyclopropane ring and the carbonyl groups are unimportant spectroscopically. This is supported by the carbonyl groups absorbing in the same position ($1695 cm^{-1}$) in the infra red spectra of both series.

Though the ultra violet curves are very similar it is possible to distinguish between the two series since in the bicyclic compounds there are peaks in the 250-5mμ. region whereas in the tricyclic series these peaks are always absent, an inflection invariably appearing at that point.

It is also interesting to note that when the substituents α to the carbonyl groups are electron attracting the short and long wavelength bands move to the visible while electron repelling groups have the opposite effect.

TABLE II

COMPOUND	λ^{1}_{max} (log ε)	λ^{2}_{max} (log ε)	λ^{3}_{max} (log ε)
	221(4.45)	249(3.94)	294(3.25)
	224(4.40)	252(3.93)	296(3.31)
	220(4.38)	254(3.89)	293(3.30)
	252(4.56)	270(4.37)	308(4.08)
	223(4.47)	-	300(3.23)
	222(4.61)	-	300(3.28)
	227(4.51)	-	304(3.39)
	227(4.47)	-	305(3.35)
	225(4.45)	-	301(3.38)
	227(4.46)	-	303(3.36)
	214(4.29)	-	330(3.55)
	208(4.38)	225(4.13)	370(3.72)
	210(4.32)	235(4.03)	380(3.79)
	210(4.48)	323(4.26)	383(3.90)

Bibliography

1. Johnson, J., 1954, 1331.
2. Chem. Ind., 1952, 855.
3. J. Amer. Chem. Soc., 1952, 74, 5683.
4. Johns, Johnson and Tisler, J., 1954, 4605.
5. Coffey, Johns and Johnson, Chem. Ind., 1955, 658.
6. Nozoe, Mukai, Ikegami and Toda, Chem. Ind., 1955, 66.
7. Buchanan, J., 1954, 1060.
8. Cook, Loudon and Steel, J., 1954, 530.
9. See 4.
10. Pauson, Chem. Rev., 1955, 55,
11. e.g. see J. Amer. Chem. Soc., 1955, 77, 116.
12. Gilman, Organic Chemistry, Wiley, 1949, Vol. I, p. 86.
13. Doering and Hoffmann, J. Amer. Chem. Soc., 1954, 76, 6162.
14. Kohler and Conant, J. Amer. Chem. Soc., 1917, 39, 1404.
15. (a) Sorrie and Thomson, J., 1955, 2238.
    (b) Idem, ibid, P. 2233.
16. Fieser and Peters, J. Amer. Chem. Soc., 1931, 53, 4080.
17. Djerassi and Lenk, J. Amer. Chem. Soc., 1953, 75, 3493.
18. e.g. see J. Amer. Chem. Soc., 1953, 75, 3513 and Chem. Ind., 1956, 847.

EXPERIMENTAL

2:3-Dihydro-2:3-methylene-1:4-naphthaquinone-2:3-dicarboxylic Acid (XXIV)

The diester (XII) (5 g.), N-bromosuccinimide (2.9 g.), and a trace of benzoyl peroxide were refluxed for 15 min. in chloroform (25 ml.) and carbon tetrachloride (25 ml.). The succinimide was filtered off and the solution washed with 5N-sodium hydroxide solution (25 ml.) and with water (25 ml.). Concentration *in vacuo* yielded the keto-ester (XXIII) (4.9 g.), m.p. 115-116° (colourless needles from ethanol) (Found: C, 64.6; H, 5.4. $C_{17}H_{16}O_6$ requires C, 64.6 H, 5.1%), $\nu_{max.}$ (in $CHCl_3$): 3070 (w), 3000 (w), 1748 (s), 1694 (s) cm^{-1}.

The ester (1 g.) was refluxed for 3 min. with 5N-sodium hydroxide (4 ml.) and ethanol (1 ml.). On acidification with hydrochloric acid (d 1.17), colourless needles of the monohydrate of the diacid (XXIV) separated, having m.p. 165-185° (decomp.) (from water) (Found: C, 56.2; H, 3.4. $C_{13}H_8O_6,H_2O$ requires C, 56.2; H, 3.6%). Recrystallisation from acetone-benzene and drying at 100°/1 mm. for 4 hr. gave faintly violet prisms of the anhydrous acid, m.p. 165-185° (decomp.) (Found: C, 60.0; H, 3.6. $C_{13}H_8O_6$ requires C, 60.0; H, 3.1%).

2:3-Dihydro-2:3-methylene-1:4-naphthaquinone (VII)

(a) To the dione (VIII) (1 g.) in carbon tetrachloride (1 ml.) was added a 10% solution of bromine in carbon tetrachloride (18.4 ml.; 2 mol.). The colour disappeared almost at once, and the solvent was removed in vacuo, leaving a yellow oil which was redissolved in acetone (25 ml.) containing sodium iodide (3 g.). After boiling for 2 hr., the solution was set aside for 3 hr. and, finally, the iodine colour was discharged by the addition of excess of aqueous sodium thiosulphate. Most of the acetone was removed in vacuo and the resulting solid was recrystallised from methanol. This gave the dione (VII) (756 mg.), m.p. and mixed m.p. 128-130°, $\nu_{max.}$ (KCl disc) 3040 (m), 1680 (s), 1000 (ms), 880 (m), 870 (m) cm^{-1}. It afforded a dioxime, m.p. 260-265° (decomp.) (from aqueous dioxan) (Found: C, 65.5; H, 5.2; N, 13.8. $C_{11}H_{10}O_2N_2$ requires C, 65.3; H, 5.0; N, 13.9%).

(b) The monoketone (XXXV) (85 mg.) in aqueous acetic acid (5 ml.; 80%) was refluxed for ½ hr. with chromic oxide (500 mg.). After being made strongly alkaline with 5N-sodium hydroxide the solution was extracted with ether (2 x 25 ml.), and the extract dried and concentrated. The product (63 mg.) was the dione, m.p. and mixed m.p. 128-130°, and its infra red spectrum (KCl disc) was identical with that

of authentic material.

2-Bromo-2:3-dihydro-2:3-methylene-1:4-naphthaquinone (XXXVII)

The dione (VIII) (50 mg.) was treated with a 10% solution of bromine in carbon tetrachloride (0.92 ml.; 2 mols.). The colour disappeared almost instantly and, after removal of the solvent in vacuo, the residual oil was taken up in ether (1 ml.) and shaken with 30% aqueous trimethylamine (1 ml.). When the ether was then removed by evaporation the crude bromo-dione (62 mg.) separated. This was filtered in benzene through neutral alumina and gave colourless prisms (from methanol), m.p. 115-116° (Found: C, 52.6; H, 3.2; Br, 31.7. $C_{11}H_9O_2Br$ requires C, 52.6; H, 2.8; Br, 31.9%), $\nu_{max.}$ (in Nujol) 1680 (s) cm.$^{-1}$. It gave a mono-oxime, m.p. 175-177° (decomp.) (Found: C, 49.4; H, 3.0; N, 5.2. $C_{11}H_8O_2NBr$ requires C, 49.6; H, 3.0; N, 5.3%).

2:3-Dibromo-2:3-dihydro-2:3-methylene-1:4-naphthaquinone (XXXIX)

(a) The dione (VIII) (100 mg.) was treated with a 10% solution of bromine in carbon tetrachloride (2.74 ml.; 3 mols.) and left until pale yellow (ca. 3 hr.); the solvent was then removed in vacuo,

and the resultant yellow oil treated with aqueous trimethylamine (2 ml.; 30%). Immediately, the dibromo-ketone was precipitated; it has m.p. 195° (decomp.), forming colourless prisms from acetone (Found: C, 40.1; H, 2.0; Br, 48.3. $C_{11}H_6O_2Br_2$ requires C, 40.0; H, 1.8; Br, 48.5%), $\nu_{max.}$ (in Nujol) 3070 (w) 1690 (s) cm^{-1}. Attempts to prepare an oxime were unsuccessful.

(b) The dione (VIII) (100 mg.) in a 10% solution of bromine in carbon tetrachloride (3.68 ml.; 4 mols.) was refluxed until the solution was pale red (ca. 5 hr.). The solvent was then removed in vacuo, and the resultant red oil was taken up in 75% aqueous acetone (4 ml.) containing potassium iodide (300 mg.). After ½ hr., excess of aqueous sodium thiosulphate was added and further dilution gave the dibromo-dione, m.p. 190° (decomp.), identical in infra red spectrum (Nujol) with that obtained above.

(c) After being kept for 5 days, a 10% solution of bromine in carbon tetrachloride (3.68 ml.; 4 mols.) containing the dione (VIII) (100 mg.) was concentrated in vacuo. The resulting oil was shaken with 30% aqueous trimethylamine (3 ml.). Immediately a dark solid separated and this was crystallised from acetone,

to give the dibromo-dione (21 mg.), m.p. and mixed m.p. 195° (decomp.).

Treatment of 4:4:6-Tribromobenzocycloheptene-3:7-dione (XXXVIII) with Alkali

The dione (VIII) (200 mg.) was set aside for 3 hr. in a 10% solution of bromine in carbon tetrachloride (5.52 ml.; 3 mols.); the solvent was then removed in vacuo, to give the crude tribromo-compound which was warmed on a steam-bath for 5 min. with 5N-sodium hydroxide (4 ml.). After filtering, the dark red solution was acidified with hydrochloric acid (5N), and the dark brown precipitate extracted with boiling water (3 x 1 ml.). The combined extracts deposited a red solid (17 mg.) on cooling. Sublimation at 130°/2 x 10^{-3} mm. gave 2-hydroxynaphtha-1:4-quinone, m.p. 190° (decomp.), identical in infra red spectrum with an authentic specimen.

5:7-Dibromo-4-hydroxy-2:3-benzotropone (XVI)

To a sublimed sample of the hydroxy-benzotropone (XI) (250mg.) suspended in glacial acetic acid (15 ml.) a 10% solution of bromine in glacial acetic acid (4.65 ml.; 2 mols.) was added, and the suspension shaken until dissolution was complete and the bromine colour had disappeared (ca. ½ hr.), then poured into water (40 ml.). The pale yellow dibromo-derivative

(460 mg.) separated. A sample sublimed at 120-140°/10^{-4}mm. had m.p. 160° (decomp.) (Found: Br, 48.1. $C_{11}H_8O_2Br_2$ requires Br, 48.2%), $\nu_{max.}$ (in Nujol) 3340 (s), 1680 (m), 1620 (s), 1590 (s), 1569 (s) cm^{-1}.

The dibromo-compound was oxidised with boiling nitric acid (d 1.2) to phthalic acid, identified as the anhydride (m.p. and mixed m.p.).

Rearrangements.

(a) The dibromo-compound (XVI) (75 mg.) was heated on the steam-bath for 15 min. with 5N-sodium hydroxide (3 ml.). The solution was then acidified and filtered, and the filtrate kept overnight. A few mg. of brown-yellow crystals separated, having m.p. ca. 180° (decomp.). Their infra red spectrum was identical with that of 2-hydroxynaphtha-1:4-quinone in almost every respect.

(b) A mixture of potassium hydroxide (900 mg.) and the dibromo-compound (XVI) (120 mg.) was heated at 110° for 10 min. After cooling, water (5 ml.) was added, and the solution acidified with hydrochloric acid (5N). Ether-extraction (2 x 20 ml.), drying, and concentration yielded a black solid which was extracted with boiling water (3 x 1 ml.). On cooling, a yellow solid (8 mg.) separated; this was sublimed

at 140°/10^{-3}mm., to give 2-hydroxynaphtha-1:4-quinone, m.p. 190° (decomp.), identical in infra red spectrum (Nujol) with an authentic specimen.

4:6-Diethoxycarboxyl-4:6-dimethylbenzocycloheptene-3:7-dione (XLVII)

The diester (XII; R = H) (5 g.) was dissolved in dry ethanol (35 ml.) containing sodium (750 mg.). After addition of methyl iodide, the solution was set aside for 24 hr., most of the solvent was distilled off, and water (200 ml.) was added. The oil which separated was taken up in ether (50 ml.), washed with 5N-sodium hydroxide solution (25 ml.), dried, and concentrated, yielding a brown solid (4.5 g,). A small portion was extracted with boiling light petroleum (charcoal) and, on cooling, colourless needles of the dimethyl-compound, m.p. 93-94°, separated (Found: C, 65.5; H, 6.7. $C_{19}H_{22}O_6$ requires C, 65.8; H, 6.4%).

4:6-Dimethylbenzocycloheptene-3:7-dione (XLVIII)

The crude ester (XLVII) (4.4 g.) was refluxed for 115 hr. with dioxan (30 ml.), water (150 ml.), and sulphuric acid (30 ml.; d 1.84). The cooled mixture was extracted with ethyl acetate (2 x 25 ml.), and the extract washed with 5N-sodium hydroxide (2 x 25 ml.).

Drying and concentration yielded a brown solid which was extracted with boiling light petroleum (charcoal). On cooling, the dimethyl-dione (715 mg.) separated as colourless prisms, m.p. 93-95° (Found: C, 76.8; H, 6.7. $C_{13}H_{14}O_2$ requires C, 77.2; H, 6.9%). It gave a dioxime, m.p. 230° (decomp.) (Found: C, 67.2; H, 6.8; N, 11.6. $C_{13}H_{16}O_2N_2$ requires C, 67.2; H, 6.9; N, 12.0%).

2:3-Dihydro-2:3-dimethyl-2:3-methylene-1:4-naphthaquinone (XLVI)

2:3-Dimethyl-naphtha-1:4-quinone (5 g.), dissolved in ethereal diazomethane (from 15 g. of N-methyl-N-nitrosourea) was kept at 0° for 4 weeks, and then concentrated. The resulting red oil was heated at 200° for 4 hr. (gas evolution) and finally distilled. The fraction, b.p. 180-190° (bath)/3.5 mm., collected as a yellow wax which was extracted with boiling light petroleum (5 x 20 ml.). Evaporation gave a yellow solid which crystallised from aqueous methanol and then from light petroleum as colourless needles of the dione, m.p. 79-80° (Found: C, 78.1; H, 5.6. $C_{13}H_{12}O_2$ requires C, 78.0; H, 6.0%), $\nu_{max.}$ (KCL disc) 3070 (w) 1675 (s) cm^{-1}. It gave a mono-2:4-dinitrophenylhydrazone, m.p. 283° (decomp.) (from nitrobenzene) (Found:

C, 59.9; H, 4.4; N, 14.7. $C_{19}H_{16}O_5N_4$ requires C, 60.0; H, 4.2; N, 14.7%), $\nu_{max.}$ (Nujol) 1675 (s) cm^{-1}. Attempts to prepare an oxime were unsuccessful.

The compound was reduced by zinc dust and acetic acid by the method described below, to give the dione (XLVIII), characterised as its oxime, identical in infra red spectrum (Nujol) with the specimen previously prepared.

(b) The dimethyl-dione (XLVIII) (100 mg.) was set aside in carbon tetrachloride (5 ml.) containing bromine (160 mg.; 2 mols.) until the colour had disappeared (ca. 1 hr.). Removal of solvent in vacuo gave an oil which was taken up in acetone (20 ml.) containing sodium iodide (300 mg.). After 3 hr. the colour was discharged with aqueous sodium thiosulphate, and removal of acetone in vacuo gave an oil which was taken up in ether (10 ml.). Drying and concentration yielded an oil which gave a 2:4-dinitrophenyl-hydrazone, m.p. 277° (decomp.) identical [mixed m.p. and infra red spectrum (Nujol)] with that obtained from the tricyclic dione (~~XLIX~~ XLVIII).

Ethyl 2-Benzylcyclopropanecarboxylates (XXXIII)

To refluxing allylbenzene (20 g.) containing copper bronze (1 g.) diazoacetic ester (30 g.) was

added dropwise during 2 hr. After refluxing for a further 2 hr. the dark mixture was filtered and steam-distilled until the distillate was clear (ca. 7 hr.). The distillate was extracted with ether (2 x 400 ml.) and, after drying and concentration, the resulting oil was distilled, giving allylbenzene (11 g.), b.p. 158-161°, and the mixture of esters (15 g.), b.p. 270-272°/754 mm., $\nu_{max.}$ (thin film) 3060 (w), 1725 (s) cm.$^{-1}$.

2-Benzylcyclopropanecarboxylic Acids (XXXIV)

The mixture of esters (XXXIII; R = Et) (15 g.) was refluxed for 30 min. with sodium hydroxide (15 g.), methanol (15 ml.), and water (50 ml.). After cooling, the solution was washed with ether (30 ml.), acidified with hydrochloric acid (5N), and extracted with ether (2 x 50 ml.). On concentration this gave an oil which was distilled, the fraction, b.p. 188-190°/16 mm. (8.6 g.), being collected as the acids.

A mixture of anilides was prepared in the usual way, giving an oil which was extracted with boiling light petroleum. Upon cooling, white needles of the cis-anilide separated, having m.p. 99-100° (Found: C, 81.0; H, 6.9; N, 5.9. $C_{17}H_{17}ON$ requires C, 81.3; H, 6.8; N, 5.6%). The remainder of the

oil was extracted with boiling light petroleum-methanol. Upon cooling, fine white needles of the trans-anilide, m.p. 124-126°, separated (Found: C, 81.2; H, 6.9; N, 5.7%). The ratio of cis/trans-isomers was ca. 10/1.

2:3-Methylene-1-tetralone (XXXV)

The mixture of acids (XXXIV) (3.6 g.) was refluxed with thionyl chloride (5 ml.) for 15 min. and excess of reagent was removed in vacuo. The acid chlorides in dry ethylene dichloride (35 ml.) containing aluminium chloride (2.80 g.) were set aside for 2 hr.; the mixture was then poured on ice (50 g.) and hydrochloric acid (20 ml.; d 1.17). The aqueous layer was removed and extracted with ethylene dichloride (25 ml.), and the combined extracts were washed with 5N-sodium hydroxide. From the latter (alkaline) extract a crude acid was isolated by acidification, ether extraction, etc. It gave only the trans-anilide, m.p. and mixed m.p. 124-126°.

Concentration of the ethylene dichloride extracts yielded an oil which was distilled. The fraction, b.p. 124-127°/15 mm. (1.53 g.) was the ketone, $\nu_{max.}$ (thin film) 1675 cm^{-1}, and gave a 2:4-dinitrophenyl-hydrazone, m.p. 226° (softens at 215°) (Found: C, 60.4; H, 3.9; N, 16.5. $C_{17}H_{14}O_4N_4$ requires

C, 60.3; H, 4.1; N, 16.6%).

Reduction of Benzocycloheptene-3:7-dione with Zinc Dust and Acetic Acid

The dione (VIII) (53mg.) was refluxed for 1½ hr. in glacial acetic acid (5 ml.) containing zinc dust (500 mg.). After being filtered and basified with 5N-sodium hydroxide the solution was extracted with ether (2 x 25 ml.) and concentrated to the oily ketol (L), $\nu_{max.}$ (thin film) 3410 (s), 1670 (s) $cm.^{-1}$ [Found: M (Rast) 204. Calc. for $C_{11}H_{12}O_2$: M, 176], which gave a 2:4-dinitrophenylhydrazone, m.p. 195° (softens at 162°) (from acetic acid) (Found: C, 57.5; H, 4.0; N, 15.6. $C_{17}H_{16}O_5N_4$ requires C, 57.3; H, 4.5; N, 15.7%), $\nu_{max.}$ (Nujol) 3485 (m) $cm.^{-1}$. The ketol also gave an oxime, m.p. 215-217° (from methanol) (Found: C, 69.2; H, 7.0; N, 7.5. $C_{11}H_{13}O_2N$ requires C, 69.1; H, 6.8; N, 7.3%).

The crude ketol [from 250 mg. of (VIII)] was set aside overnight in 80% aqueous acetic acid (7 ml.) containing chromic oxide (500 mg.), then basified with 5N-sodium hydroxide solution, and extracted with ether (2 x 25 ml.); concentration yielded an oil which gave the bis-2:4-dinitrophenylhydrazone, m.p. 248-250° (decomp.) (from nitrobenzene),

of the dione (VIII) (Found: C, 51.5; H, 3.6; N, 21.0. $C_{23}H_{18}O_8N_8$ requires C, 51.7; H, 3.6; N, 20.9%), identical in infra red spectrum with that prepared from an authentic sample of the dione (VIII).

Reduction of the Methylenenaphthaquinones with Zinc Dust and Acetic Acid

The dione (VII) (200 mg.), the bromo-dione (XXXVII) (200 mg.), and the dibromo-dione (XXXIX) (200 mg.) were each reduced in boiling glacial acetic acid (10 ml.) containing zinc dust (750 mg.), and the products isolated as in the previous experiment and characterised as the 2:4-dinitrophenyl-hydrazone of the ketol (L) [mixed m.p.s and infra red spectra (Nujol)].

Reduction of 2:3-Diethoxycarbonyl-2:3-dihydro-2:3-methylene-1:4-naphthaquinone (XXIII) with Zinc Dust and Acetic Acid

The keto-ester (XXIII) (300 mg.) was refluxed in glacial acetic acid (10 ml.) containing zinc dust (600 mg.) for 2½ hr. Filtration and dilution gave a small quantity of a sticky solid which was dissolved in ether (5 ml.) and extracted with 5N-sodium hydroxide (3 ml.). Acidification of the extract gave a white solid, m.p. 83-85° (from light petroleum), undepressed in mixed m.p. with the ester (XII:R=H).

4:6-Diethoxycarbonyl-3:7-diacetoxybenzocyclohepta-1:3:6-triene (XII; R = Ac)

Acetyl chloride (5 ml.) was added dropwise during 10 min. with shaking and cooling to the diester (XII; R = H) (5 g.) in dry pyridine (15 ml.). Next morning the solid was filtered off and washed with dry ether (50 ml.), and the ethereal solution extracted with hydrochloric acid (4 x 50 ml.; 5N), sodium hydroxide solution (4 x 50 ml.; 5N), and water (50 ml.). Drying and concentration gave the enol acetate (6.0 g.) as an oil which solidified, m.p. 91-92° (prisms from ether) (Found: C, 63.0; H, 5.5. $C_{21}H_{22}O_8$ requires C, 62.7; H, 5.5%), $\nu_{max.}$ (in CCl_4) 1774 (s), 1710 (s), 1285 (s) 1210 (s) cm.$^{-1}$.

4-Hydroxy-2:3-benzotropone (XI)

The diacetate (XII R = Ac) (3.0g.) and N-bromo-succinimide (2.1 g.) in carbon tetrachloride (50 ml.) was refluxed for 1 hr. with a trace of benzoyl peroxide. Washing with water (3 x 25 ml.) and concentration in vacuo yielded a pale yellow oil which, on addition of 5N-sodium hydroxide (10 ml.), gave an extremely insoluble sodium salt. Acidification of a small quantity of this salt with hydrochloric acid (d 1.17) afforded the pale yellow diester (XIII), m.p. 74-75° (prisms from hexane) (Found: C, 64.5; H, 5.1.

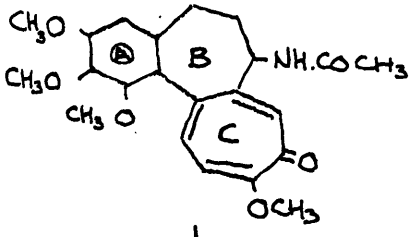
$C_{17}H_{16}O_6$ requires C, 64.5; H, 5.1%), $\nu_{max.}$ (in CCl_4) 2950 (w), 1710 (s), 1650 (s), 1620 (m) cm^{-1}.

Hydrolysis of the remainder of the salt with 5N sodium hydroxide (50 ml.) and ethanol (10 ml.) gave a dark brown solution, which, on acidification with hydrochloric acid (d 1.17), evolved carbon dioxide and gave the yellow 4-hydroxy-2:3-benzotropone (1.3 g.), m.p. 175-180°. A sample sublimed at 150-160°/10^{-4}mm. had m.p. 183-185° (Found: C, 76.4; H, 5.1. $C_{11}H_8O_2$ requires C, 76.7; H, 4.7%), $\nu_{max.}$ (in $CHCl_3$): 3175 (m), 1698 (s), 1650 (s), 1593 (s), 1570 (s) $cm.^{-1}$, $\nu_{max.}$ (Nujol): 3300-2060 (m), 1610 (w), 1540-1470 (s), 1330 (s), 1240 (s), 786 (m), 760 (s) $cm.^{-1}$.

Part II

A Synthetic Approach to Colchicine

The structure of the alkaloid colchicine is now firmly established as (1) but all evidence relating to the structure of ring C is purely degradative and,



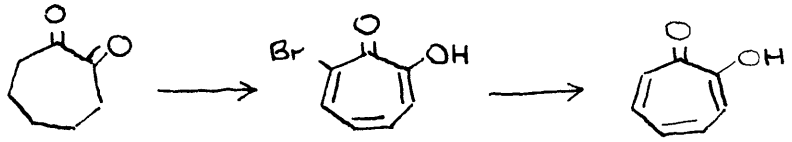
1

to date, no degradation product containing the seven membered ring C has been synthesised so it is desirable that the molecule be synthesised.

Most of the work reported up to the present on synthetic approaches to colchicine has been directed to the preparation of compounds containing the carbon skeleton rather than to the synthesis of the molecule itself. Indeed most of the methods used are patently inapplicable to a synthesis of the alkaloid.

Generally speaking the most difficult stage of any synthesis of colchicine would appear, on paper at least, to be the construction of the tropolone

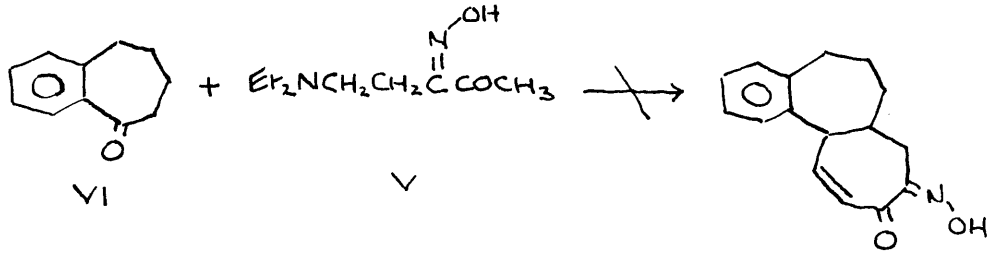
ring C, since the available methods seem ill suited for use in a long synthesis because of the difficulty of making the required intermediates and the low yields usually encountered in the last stages of the syntheses. The simplest and most direct of the published methods of making tropolone[2] (IV) is by



II III IV

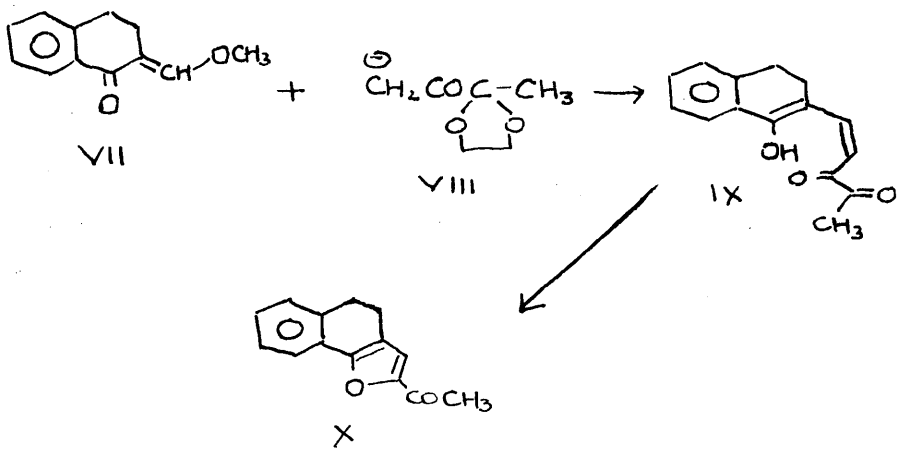
the bromination/dehydrobromination of cycloheptan-1:2-dione (II) to yield 3-bromotropolone (III) which can be hydrogenolysed to tropolone (IV); but even in this method the yields are not outstanding and cyclo-heptan-1:2-diones, especially unsymmetrical ones, are not readily accessible.

Two unsuccessful attempts to make a tropolone ring by a method which could be applied to colchicine have been reported. In the first[3] the Mannich base (V)



VI V

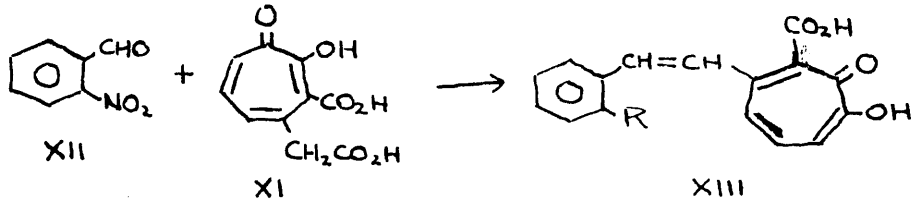
was condensed with benzsuberone (VI) in the hope of effecting a Robinson-Mannich type of reaction yielding the oximino ketone shown, but no useful product could be isolated. In another similar approach[4] the enol ether (VII) was condensed with the enolate (VIII) to give the Michael adduct (IX) which on acid catalysed ring closure yielded, not



the tropolone, but the furan (X). When base catalysed cyclisation was tried benzylic acid rearrangement of the 1:2-dione system occurred.

One approach studied[5] involved the use of a preformed tropolone ring, viz. (XI), which condensed

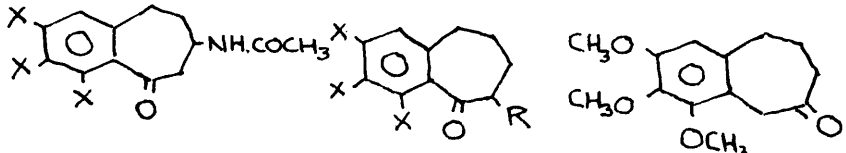
with o-nitrobenzaldehyde (XII) with concomittant decarboxylation to yield the olefin (XIII: R = NO_2).



The nitro group was reduced to yield the amino compound (XIII: R = NH_2) which resisted all attempts to cyclise it by the Pschorr method. The olefins (XIII) were thus assigned to the <u>trans</u> series in which cyclisation is sterically impossible. No successful condensation of the tropolone (XI) with o-nitrophenylacetaldehyde was reported although from the point of view of a colchicine synthesis this would be the more accurate analogy.

Some other approaches attempted to synthesise compounds containing rings A and B of the molecule on the which ring C might be built. The synthesis of the ketone (XIV: X = H) has been reported[6] but attempts to make (XIV: X = OCH_3) by the same method

failed at the penultimate stage. However an



XIV XV XVI

investigation of ketones of that type showed them to be unsuitable for the kind of reactions envisaged since (XV:X = OCH_3; R = $CH_2CO_2CH_3$) proved to be extremely sluggish in carbonyl reactions[7] e.g. it did not undergo the Reformatsky reaction. As the ketoester (XV:X = H; R = $CH_2CO_2CH_3$) readily underwent carbonyl additions the unreactivity of the former is undoubtedly due to steric hinderance of the carbonyl by the peri methoxyl group.

Another ketone (XVI) has also been synthesised[8] but the route is long and tedious though recently two shorter syntheses of this compound have been reported[9,10]. No reports of the chemistry of this ketone have been made.

In our approach it was decided to use a ketone of the latter type, viz. (XVII), as an intermediate

and to attempt to elaborate ring C on to that framework.

The Synthesis of the Intermediate Ketone (XVII) (see P60a Sheet V)

In chosing a route to our intermediate the unsaturated ketone (XXI) looked to be a promising starting material, especially as we believed that reactions involving enolisation of the carbonyl group would occur at the allylic, rather than benzylic, methylene group.

Eschenmoser and his coworkers prepared (XXI)[10] by the following route. Purpurogallin tetramethyl ether (XVIII) was reduced by lithium aluminium hydride to the alcohol (XIX) and on treatment with sulphuric acid a facile dehydroxylation occurred yielding a red solution of the tetramethoxybenztropylium ion (XX). Upon reduction with zinc dust in sulphuric acid under carefully controlled conditions the unsaturated ketone (XXI) was obtained. Its structure followed from its ultra violet and infra red spectra and its reduction to the known dihydroketone (XVI).

We found that reduction of the tetramethyl ether (XVIII) went as readily with methanolic sodium borohydride as with lithium aluminium hydride but that the zinc dust reduction of the tropylium ion from both sources was extremely capricious and we were unable to get reproducible results even with the use of zinc dust activated in a standard manner.

On some occasions the oily product from the reduction contained little or no carbonyl material so it was decided to investigate the structure of the unwanted product in the hope that knowledge of its genesis might help us to modify the conditions of reaction to increase the yield of the desired ketone.

A pure sample of the by-product was separated from the carbonyl compound by use of Girard's Reagent P and purified by chromatography and distillation. It analysed for $C_{14}H_{18}O_3$, had an ultra violet spectrum almost identical with that of the ketone (XXI), and upon catalytic hydrogenation absorbed one mole of hydrogen giving a compound whose ultra violet spectrum was very similar to that of (XVI). Thus it was formulated as (XXII) and this structure was conclusively proved by its oxidation to the known dicarboxylic acid

(XXIV) with cold neutral potassium permanganate solution. That the olefin (XXII) is indeed formed by a Clemensen-like reduction of the ketone (XXI) and not by an alternate mode of reduction of the ion (XX) is demonstrated by the conversion of the ketone (XXI) to the olefin under the conditions of the original reduction. It is not quite clear why this reduction should occur under such mild conditions (zinc dust and 25% sulphuric acid at 40°C).

We now turned to alternative methods of reduction. Firstly the concentration of acid was varied and it was found that with 15% sulphuric acid slightly better yields were obtained but the reaction was still unsatisfactory and could not be carried out reproducibly on the large scale required.

Addition of a little acetic acid to the reaction mixture caused the reduction to go much more rapidly but gave intractable products as did variation of reaction temperatures.

Variations in the reducing agent were tried but with no attendant success. With iron or aluminium at 15°, 40°, and 90° reduction took place but the products were intractable gums which contained none

of the desired ketone (infra red spectra) nor could any crystalline derivatives be prepared. Under the same conditions tin and stannous chloride caused no reduction and the ion was also stable to hydrogen in the presence of Adam's catalyst.

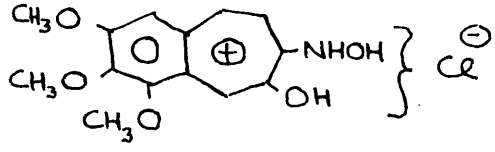
An obvious method of obtaining the ketone (XXI) is by Wulff-Kishner reduction of the tetramethylether (XVIII) but under the conditions tried only dark intractable materials were obtained which gave no carbonyl derivatives.

As the hydroxyl group in the alcohol (XIX) is both allylic and benzylic it should be susceptible to ready hydrogenolysis. It was therefore reacted with one mole of sodium in liquid ammonia, but the product gave no carbonyl reactions indicating that the diene system was reduced more readily than the hydroxyl. The alcohol was stable to zinc dust in ethanol.

Although our efforts to obtain the ketone (XXI) in good yield had been fruitless it was decided to carry on and investigated its chemistry. Our belief that reactions involving enolisation of the carbonyl group would take place at the allylic methylene was supported by the oxidation of the ketone (XXI) by Eschenmoser and coworkers to the tropolone[10] (XXIX: R = H).

First we reacted the unsaturated ketone (XXI) with one mole of N-bromosuccinimide hoping to introduce a bromine atom which could then be displaced by a nitrogenous compound such as potassium phthalimide but the results of the reactions were indeterminate owing to the ready decomposition of the bromination product.

We then turned to nitrosation as a method for introducing the required nitrogen. Results were unpromising with sodium ethoxide and amyl nitrite but reaction of the ketone (XXI) with the latter and dry hydrogen chloride[12] in ether gave a bright yellow hydrochloride of surprising stability (unhydrolysed by boiling water). This prompts us to represent it as (XXXII) rather than (XXV) or better, perhaps, to take the view that these two formulae represent limiting structures of a resonance stabilised molecule.



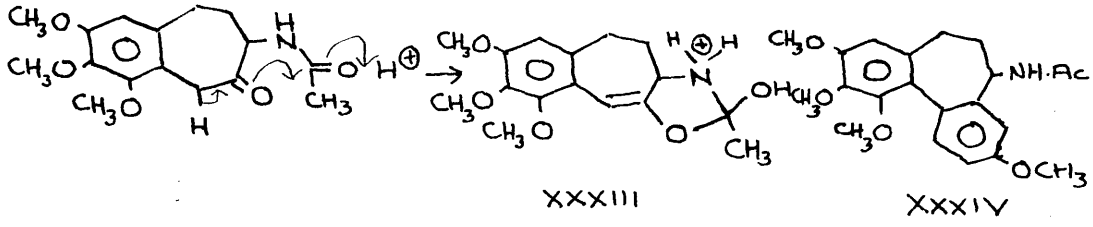
XXXII

It titrated as a dibasic acid with phenolphthalein as indicator, gave a deep red color in alkali, and a precipitate with silver nitrate. Surprisingly the ultra violet spectrum in alkaline solution is remarkably similar to that of the ion (XX). Why this should be so is not at all obvious.

Upon catalytic hydrogenation in the presence of Adam's platinum oxide the hydrochloride (XXV) absorbed three or more moles of hydrogen depending on the quality of the catalyst. If reduction was stopped after the absorption of three moles a crude amino-ketone hydrochloride (XXVII) resulted, which, upon basification, yielded the dihydropyrazine (XXVIII) demonstrating that it was an α-amino ketone. The dihydropyrazine was unstable and cannot, on the basis of analysis, be distinguished from the fully aromatic pyrazine, but its ultra violet spectrum showed no absorption characteristic of the latter.

Acetylation of the hydrochloride (XXVII) with hot acetic anhydride yielded the ketone (XVII) whose structure was supported by its infra red and ultra violet spectra. Unexpectedly it was soluble in 5N hydrochloric acid and was reprecipitated with 5N sodium

hydroxide. This may be a physical solubility but it is possible that it exists as (XXXIII) in acid



XXXIII XXXIV

solution; the amide forming an ortho ester type of intermediate as in N→O acyl migrations.

After the failure of some attempts to prove the structure of the acetamido ketone (XVII) by converting it into N-acetylcolchinol methyl ether (XXXIV) we decided to undertake an unambiguous synthesis.

As mentioned before the unsaturated ketone (XXI) is oxidized with selenium dioxide to the tropolone (XXIX; R = H). This substance is inert towards carbonyl reagents, but the benzyl ether (XXIX: R = CH_2Ph), prepared by reaction of benzyl bromide with the tropolone in methanolic sodium methoxide, readily yields an oxime (XXX) which was reduced with Adam's catalyst and hydrogen in acetic anhydride to the ketone (XVII) identified as the 2:4-dinitrophenylhydrazone

by m.p., mixed m.p., and infra red spectrum.

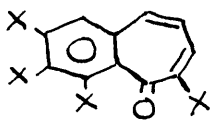
To return to the hydrochloride (XXV). In the hope of orienting the oximino group it was warmed with 40% aqueous formaldehyde and 1N hydrochloric acid[12] to hydrolyse the oxime to a carbonyl group but instead of the expected tropolone (XXIX: R = H) a dark red solid, $C_{15}H_{15}O_5N$, was isolated. It could be obtained in better yield by reacting the hydrochloride with formaldehyde alone. On the basis of its analysis, its yellow hydrochloride, and the absence of any absorption in its infra red spectrum in the 3600-3100cm^{-1} region we regard (XXVI) as a possible structure for this deep red product. However on the basis of this the benzyl ether (XXX) might be expected to be red also - it is yellow, but the ultra violet spectra of the two compounds in the 200-400 mu . region are similar and the red color of (XXVI) is due to a low intensity band at long wavelengths which might arise from the heterocyclic ring in (XXVI).

Some Attempts to Alkylate the Ketone (XVII)

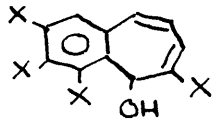
Having synthesised the ketone (XVII) and firmly established its structure it was now our intention to build on ring C using the reactive benzylic methylene and the carbonyl groups as points of attachment as in

SHEET V

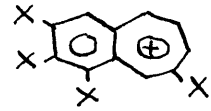
$X = -OCH_3$



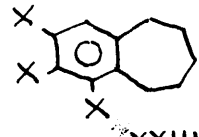
XVIII



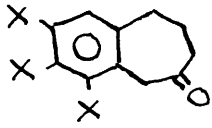
XIX



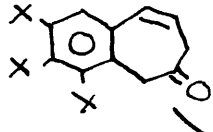
XX



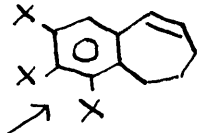
XXIII



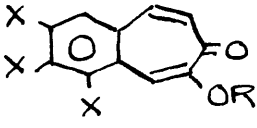
XVI



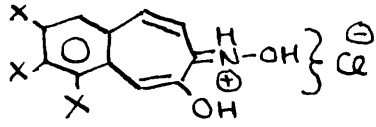
XXI



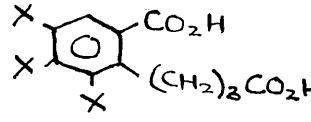
XXII



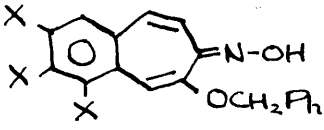
XXIX



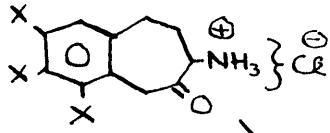
XXV



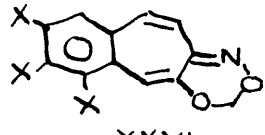
XXIV



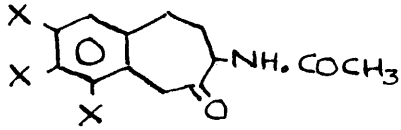
XXX



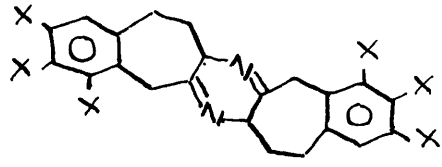
XXVII



XXVI

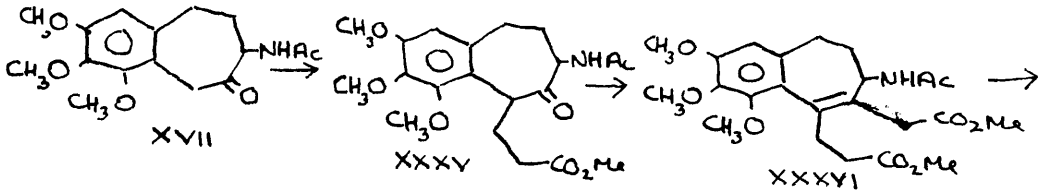


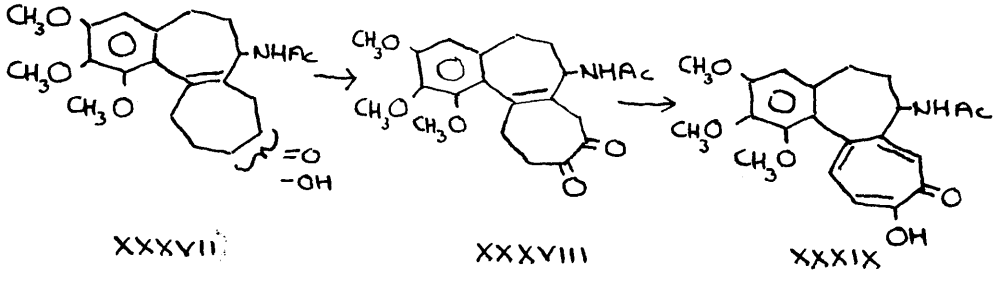
XVII



XXVIII

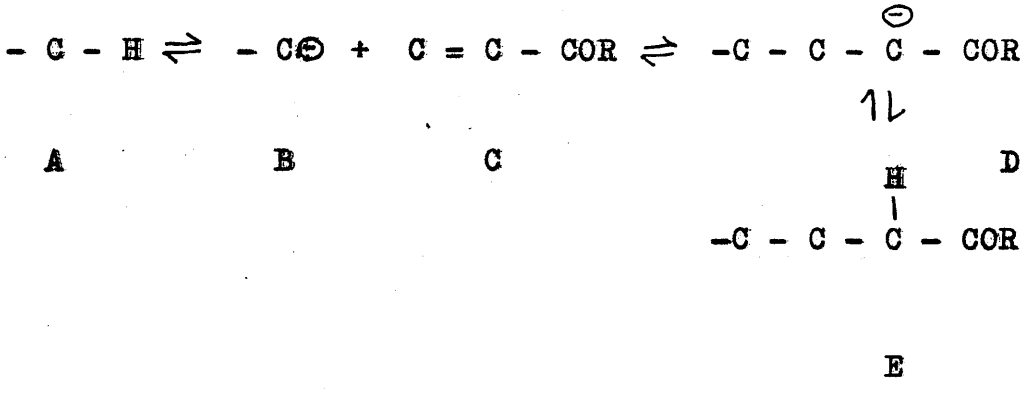
the scheme below. It was envisaged that the





ketone (XXII) would yield a Michael adduct (XXXV) and then a two carbon fragment would be introduced at the site of the carbonyl group to give (XXXVI). Cyclisation of the diester by the acyloin method should yield (XXXVII) which after oxidation to (XXXVIII) would be readily converted to colchicine (XXXIX).

In fact we were unable to effect even the first stage of the synthetic scheme. Generally speaking there are two distinct methods of carrying out a Michael reaction which is the addition of a carbanion to the β position of a double bond conjugated to an unsaturated grouping such as CO, CN, CO_2R and which can be represented as shown. In the first

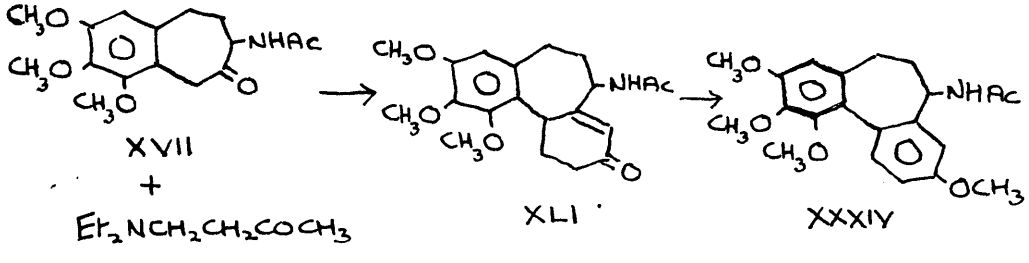


general method the acidic compound, A, is reacted with one mole of strong base to form the carbanion, B, which then adds to the electrophile, C, to yield the carbanion of the adduct, D. Protonation in the working up then gives the addend, E. All the stages are reversible in principle but in the presence of strong base almost all of A is converted to B and protonation of D does not occur during the reaction

so that the extent to which addition takes place will depend on the position of equilibrium between B + C and D i.e. addition will occur only if the carbanion D is more stable than the carbanion B.

In the second method only a catalytic quantity of base is used so that the carbanions B and D have only a transient existence and the extent of reaction depends on the position of equilibrium between the neutral molecules A + C and E enabling the equilibrium to be shifted to the favorable side by use of a large excess of one of the starting materials.

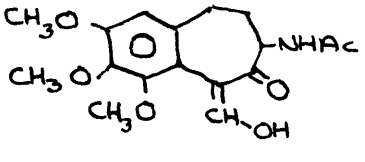
With these factors in mind our initial attempts, as mentioned before, were directed towards converting the ketone (XVII) into N-acetylcolchinol methyl ether (XXXIV) by means of a Robinson-Mannich reaction, followed by dehydrogenation and methylation.



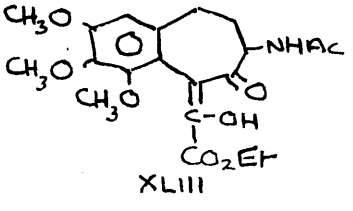
However under the conditions used by us (see Table III) reaction of the acetamido ketone (XVII) with diethylaminobutanone or its methiodide yielded neither the ketone (XLI) nor its precursors.

Similar lack of success attended our attempts to alkylate the ketone (XVII) with methyl acrylate, β-bromopropionic ester, and acrylonitrile using various catalysts (see Table III). Lack of success under conditions of strong base catalysis with one mole is not surprising since one would expect the enolate of the ketone (XVII) to be more stable than the carbanion of the adduct which is only stabilised by a methoxcarbonyl group.

Unsuccessful attempts were also made to activate the receptor methylene group by condensing (XVII) with ethyl formate to yield (XLII) or with ethyl oxalate to give (XLIII). Only dark unstable gums were obtained.

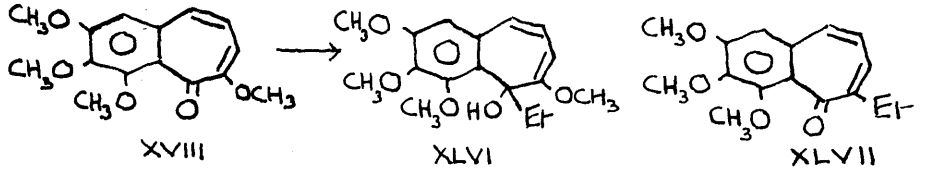


XLII



XLIII

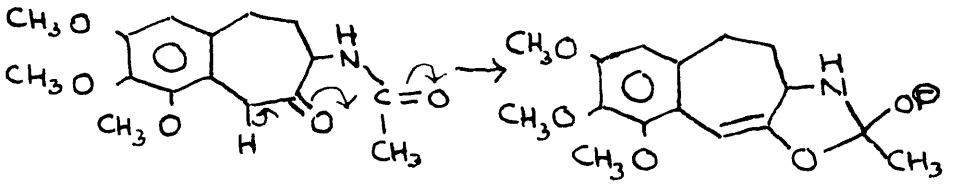
In an effort to introduce the side chain at an earlier stage purpurogallin tetramethyl ether (XVIII) was reacted with ethyl magnesium bromide in the hope of getting the alcohol (XLVI) which would



XVIII XLVI XLVII

be processed in the same way as the alcohol from the reduction of (XVIII). However only a trace of (XLVI) (based on the formation of tropylium ion) was produced and the main product analysed for (XLVII) but was not more fully investigated.

Our lack of success in the alkylation reactions may be due to our use of inappropriate reaction conditions, but it is also possible that the reason is inherent in the molecule and that the enolate formed interacts with the acetamido group as shown

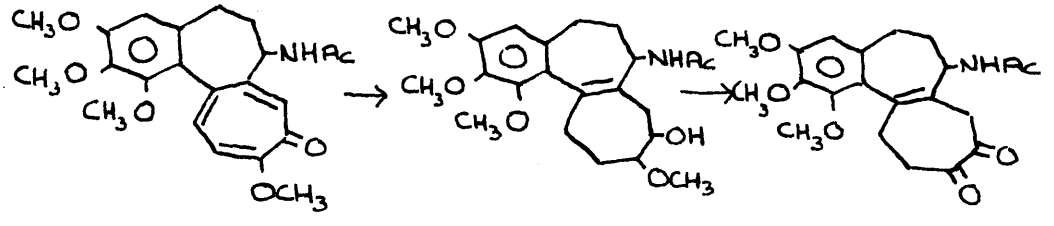


XLVIII

to yield (XLVIII) which would not alkylate normally.

Some Attempts to Prepare a Relay

Concurrently with our synthetic work we carried out some experiments on colchicine (1) and its derivatives in an effort to obtain the α-diketone (XXXVIII), an intermediate in our synthetic route which could be oxidized by scission of the 1:2-dione



I XLIV XXXVIII

system to a dicarboxylic acid also an intermediate in the proposed synthesis.

The most promising starting material seemed to be the alcohol (XLIV) prepared[12] by catalytic hydrogenation of colchicine (1). Here again we were unsuccessful since we were unable to oxidize (XLIV) to the ketone using chromium trioxide in pyridine, potassium tertiary-butoxide and benzophenone in benzene, chromic acid in acetone, Raney nickel and cyclohexanone in toluene, or aluminium tertiary-butoxide and acetone in benzene. In most cases intractable materials from which no carbonyl derivatives could be prepared were isolated.

Attempts to partially hydrogenate colchicine (1) using Adam's catalyst in acetic acid or sodium in liquid ammonia also lead to unusable products.

Bibliography

1. See Manske and Holmes, "The Alkaloids," Vol.II.,p.261.
2. Cook, Gibb, Raphael and Somerville, J., 1951, 503.
3. Tarbell, Wilson and Ott, J. Amer. Chem. Soc., 1952, 74, 6263.
4. Ott and Tarbell, ibid., 1952, 74, 6266.
5. Tarbell, Smith and Boekelheide, ibid., 1954, 76, 2470.
6. Horton and Thompson, ibid., 1954, 76, 1909.
7. Anderson and Greer, ibid., 1952, 74, 5203; 1953, 75, 4976.
8. Rapoport and Campion, ibid., 1951, 73, 2239.
9. Walker, ibid., 1955, 77, 6699.
10. Schaeppi, Schmidt, Heilbronner and Eschenmoser, Helv. Chim. Acta, 1955, 38, 1874.
11. Hawarth, Moore and Pauson, J., 1948, 1045.
12. Barltrop, Johnson and Meabins, J., 1951, 181.
13. Windaus, Annalen, 1924, 439, 59.

Experimental

Reduction of 4:2′:3′:4′- Tetramethoxybenzocyclo-heptatrienylium Sulphate (XX)

The reduction was carried out as previously described[10] and the oily product (5.98 g.) was separated with Girard's reagent P into the ketone (XXI) (1.8 g.) m.p. 70-72° (cyclohexane) [light absorption in ethanol; $\lambda_{max.}$ (log ε), 224 (4.4), 258 mμ (3.98)] and the styrene (XXII) (1.6 g.) which was filtered through neutral alumina in benzene, and distilled at 165-170°/0.08 mm. as a colourless oil (Found: C, 71.4; H, 7.6. $C_{14}H_{18}O_3$ requires C, 71.8; H, 7.7%) [light absorption in ethanol: $\lambda_{max.}$ (log ε), 223 (4.48), 263-264 mμ (4.05)].

2′:3′:4′-Trimethoxybenzocycloheptene (XXIII)

The styrene (XXII) (300 mg.) rapidly absorbed 1 mol. of hydrogen in ethanol (15 ml.) in the presence of 2% Pd-$CaCO_3$ (200 mg.). After filtration, concentration yielded the dihydro-derivative, b.p. 155-160° (bath)/0.3 mm., m.p. 44-48° (Found: C, 70.9; H, 7.7. $C_{14}H_{20}O_3$ requires C, 71.2; H, 8.5%). Light absorption: $\lambda^{EtOH}_{max.}$ (log ε) 274 mμ (3.33).

Oxidation of 1′:2′: 3′- Trimethoxybenzocyclohepta-1:3-diene (XXII)

The styrene (XXII) (500 mg.), in water (20 ml.),

was shaken with portions of solid potassium permanganate until the mother liquors were permanently pink. After filtration, the filtrate was continuously extracted with ether for 4 hr. The product had m.p. 135-137° (from water) (Found: C, 56.6; H, 6.1%; equiv., 147. $C_{14}H_{18}O_7$ requires C, 56.4; H, 6.1%; equiv., 149). Light absorption: $\lambda_{max.}^{EtOH}$ (log ε), 252 (4.02), 294 mμ (3.52). Mixed m.p. and infra red spectra showed it to be identical with a sample synthesised by Haworth's method[11].

4-Hydroxy-5-hydroxyimino-2′:3′: 4′-trimethoxybenzocyclohepta-1:3:6-triene (XXV).

The ketone (XXI) (3.6 g.) in ether (50 ml.) was cooled in ice and treated with dry hydrogen chloride, whilst amyl nitrite (4 g.) in ether (20 ml.) was added dropwise. The yellow precipitate (2.69 g.) was filtered off; it had m.p. 206-208° (decomp.) (from ethanol) (Found: C, 53.6; H, 4.9; N, 4.5; Cl, 11.1%; equiv., 156. $C_{14}H_{16}O_5NCl$ requires C, 53.6; H, 5.1; N, 4.5; Cl, 11.3%; equiv., 157). Light absorption in ethanol: $\lambda_{max.}$ (logε), 258 (4.46), 338-339 (3.87), 355 (3.75), 383 mμ (3.51); in alcoholic alkali, 241 (4.10), 271 (4.25), 321 (4.48), 391 (3.88), 460 mμ (3.57).

When the hydrochloride (184 mg.) was warmed for 5 min., with aqueous formaldehyde (40%; 1.5 ml.), with or without 5N-hydrochloric acid, and finally diluted, there was formed a flocculent red precipitate (68 mg.). The product crystallised in small red needles from ethanol; it had m.p. 168-170° (Found: C, 62.0; H, 4.9; N, 5.1. $C_{15}H_{15}O_5N$ requires C, 62.3; H, 5.2; N, 4.8%). Light absorption in ethanol: $\lambda_{max.}$ (log ε), 257 (4.45), 320 (4.54), 365 (4.12), 384 mμ (4.16); in acidified ethanol, 258 (4.42), 320 (4.54), 365 (3.99), 383 (4.01), 436 mμ (3.75).

5-Acetamido-4-oxo-2′:3′: 4′-trimethoxybenzocycloheptene (XVII)

(a) The hydrochloride (1 g.) in ethanol (20 ml.) containing Adam's platinum oxide catalyst (200 mg.) was shaken with hydrogen until 3 mols. had been absorbed, and was then filtered. Concentration of the filtrate yielded a dark glass which was warmed on the steam-bath for 10 min. with acetic anhydride (5 ml.), and concentrated in vacuo. The resulting dark oil afforded the ketone (XVII) (617)mg.), m.p. 157-159°, as needles from acetone (Found: C: 62.6; H, 6.3; N, 4.9; MeO, 30.0; AcO, 13.5. $C_{16}H_{21}O_5N$

requires C, 62.5; H, 6.8; N, 4.6; 3MeO, 30.3; 1AcO, 14.0%). Light absorption in ethanol: $\lambda_{max.}$ (logε), 278-280 mμ (3.17); $\nu_{max.}$ 1710 cm^{-1}. It gave a 2:4-dinitrophenylhydrazone, m.p. 260-261° (decomp.), as yellow prisms from acetic acid (Found: C, 54.5; H, 5.1; N, 14.5. $C_{22}H_{25}O_8N_5$ requires C, 54.2; H, 5.1; N, 14.4%).

When a small portion of the above glass, in ethanol, was treated with 5N-sodium hydroxide solution, a white precipitate formed. Rapid crystallisation from ethanol gave the dihydropyrazine (XXVIII) as prisms, m.p. 230° (decomp.) (Found: C, 67.8; H, 7.1; N, 5.4. $C_{28}H_{34}O_6N_2$ requires C, 68.0; H, 6.9; N, 5.7%). Light absorption in ethanol: $\lambda_{max.}$ (logε), 278 mμ (3.47).

(b) The hydroxyimino-ether (XXX) (39 mg.) in acetic anhydride (2 ml.) was shaken with hydrogen in the presence of Adam's platinum oxide catalyst (11 mg.). After the absorption of 4 mols. of hydrogen the solution was filtered. Concentration gave an oil which furnished a 2:4-dinitrophenylhydrazone, identical in m.p. and mixed m.p. and in its infra red spectrum with that described above.

4-Benzyloxy-5-hydroxyimino-2′: 3′: 4′-trimethoxybenzocyclohepta-1:3:6-triene (XXX)

The tropolone (XXIX; R = H) (120 mg.) was set aside overnight in methanol (15 ml.) containing sodium (11 mg.) and benzyl bromide (500 mg.). The solution was concentrated in vacuo, water added, and the suspension extracted with ethyl acetate. Concentration of the extract yielded an oil which was washed with petrol (b.p. 40-60°), and the residue crystallised from petrol (b.p. 60-80°), to give the ether (XXIX; R = $PhCH_2$), m.p. 98-100° (Found: C, 71.25; H, 5.8. $C_{21}H_{20}O_5$ requires C, 71.6; H, 5.7%).

The ether was converted into the oxime (XXX), m.p. 171-172°, in the usual manner (Found: C, 68.8; H, 5.7; N, 4.0. $C_{21}H_{21}O_5N$ requires C, 68.65; H, 5.8; N, 3.8%). Light absorption in ethanol: $\lambda_{max.}$ (log ε) 255 (4.55), 288 (4.30), 337 mμ (3.72).

Table III

Reaction of ketone (XVII) with $Et_2\overset{\oplus}{N}(CH_3)CH_2CH_2COCH_3\}\ I^-$

	Conditions	Product
1.	Excess NaOMe in MeOH for 24 hr at 15°	Intractable oil
2.	" " " " " " " " 75°	" "
3.	" $KOBu^t$ " Bu^tOH " " " " " 15°	" "
4.	" " " " " " " " 80°	" "
5.	" " " PhH " " " " "	" "
6.	" NaOMe " " " " " " "	Starting Material

Reaction of ketone (XVII) with $Et_2NCH_2CH_2COCH_3$

	Conditions	Product
1.	Drop of Piperidine in PhH for 24 hr. at 80°	Starting Mat.
2.	Excess $KOBu^t$ " " " " " " 15°	" "
3.	" " " " " " " " " 80°	Intractable oil

Reaction of ketone (XVII) with 20 fold excess of

$CH_2 = CH.CO_2Me$

	Conditions	Product
1.	Excess NaOMe in PhH for 24 hr. at 15°	Starting Material
2.	" " " " " " " " 80°	Intractable Oil
3.	" " " MeOH " " " " 15°	Starting Material
4.	" " " " " 4 Hr. " 75°	Intractable Oil
5.	Trace of " " " " 24 hr. " 15°	Starting Material
6.	" " " " " " 11 hr. " 75°	Intractable Oil

Table III (contd.)

	Conditions					Product
7.	Trace of Piperidine	in	PhH	for 24hr.	at 80°	Starting Material
8.	" " $KOBu^t$	"	Bu^tOH	" 4hr.	" "	Intractable Oil
9.	" " "	"	"	" 24hr.	" 15°	Starting Material
10.	Drop " Triton B	"	"	" 24hr.	" "	" "
11.	" " " "	"	"	" 4hr.	" 80°	" "

Reaction of Ketone (XVII) with 10 fold excess of

$BrCH_2CH_2CO_2Me$

	Conditions					Product
1.	Excess $KOBu^t$	in	PhH	for 24hr.	at 15°	Starting Material
2.	" NaH	"	"	" 3hr.	" 80°	" "
3.	" $KOBu^t$	"	"	" 5hr.	" "	Intractable Oil
4.	" $NaNH_2$	"	"	" 3hr.	" "	Starting Material

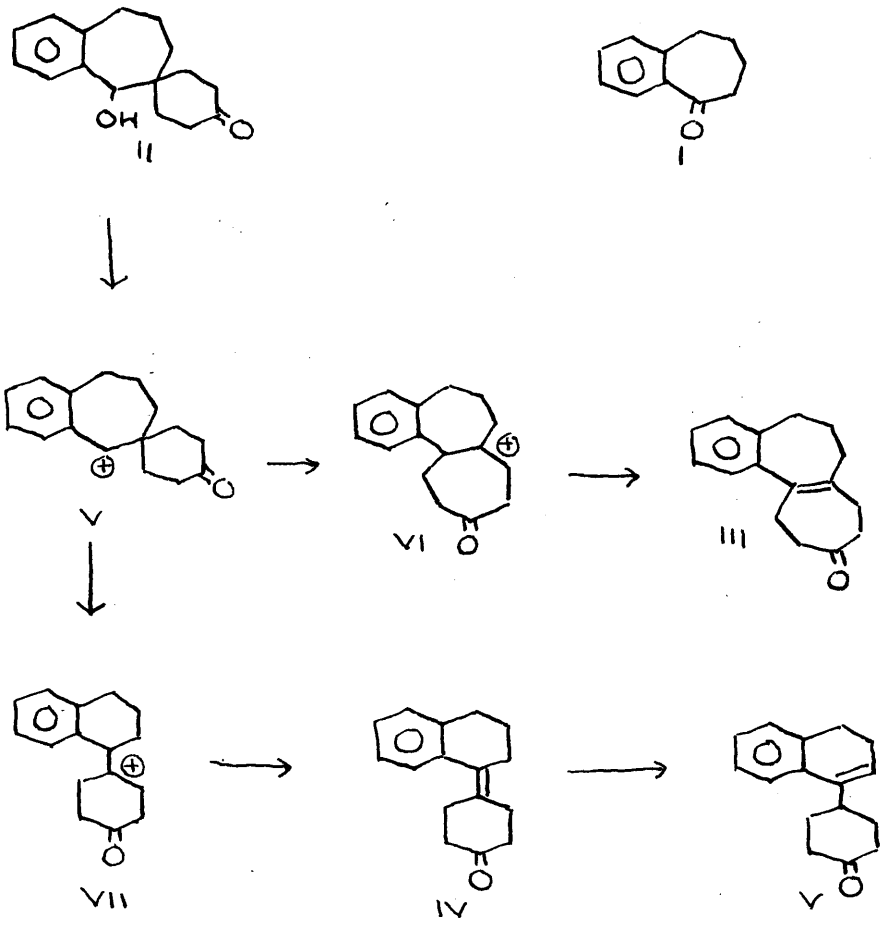
Reaction of Ketone (XVII) with 10 fold excess of CH_2=CHCN

	Conditions					Product
1.	Drop of Triton B	in	Bu^tOH	for 2hr.	at 15°	Intractable Oil
2.	Trace of NaOEt	"	EtOH	" "	" "	Starting Material
3.	" " "	"	"	" "	" 80°	" "
4.	" " $KOBu^t$	"	Bu^tOH	" 3hr.	" 15°	" "
5.	" " "	"	"	" "	" 80°	" "

Some Experiments Designed to Lead to the Colchicine Carbon Skeleton

With the abandonment of our previous synthetic route to colchicine we now turned to other methods still starting from a molecule containing rings A and B of colchicine.

Owing to the difficulty of obtaining the requisite starting material and doubt that one of the reactions involved would take the desired course, we determined to use benzsuberone (1) as a model compound on which to explore our route. If this compound is to be used as an accurate model it is obvious from the previous discussion that reactions involving the carbonyl group must be susceptible to little steric hinderance and, since complex metal hydride reduction comes into this category[1], we decided to make the ketol (II) and determine whether a Wagner-Meerwein rearrangement[2] on it would give the compound with the desired carbon skeleton (III) or the alternative product of migration (IV). In this manner we would overcome the difficulties inherent in making seven membered rings by direct cyclisation.



If the rearrangement is concerted i.e. if extrusion of the hydroxyl group is synchronous with migration of the alkyl chain, the structure of the product will depend on which alkyl group is <u>trans</u> to the hydroxyl. In the ketol (II) there are two relevant conformations

which can be written, one which would lead to (VI) and the other to (VII). In the first case the C-C bond of the six membered ring is trans to the hydroxyl and, in the other, the relevant C-C bond of the seven membered ring is the one which should migrate most readily. However the steric interactions in the two conformational isomers are sufficiently delicately balanced to make deduction of which is the more stable difficult.

It is quite likely that the process is not a synchronous rearrangement and that the primary product of reaction is the carbonium ion (V) which can rearrange to (VI) or (VII) which then lose a proton to give (III) in one case or, in the other, (IV) which will probably be unstable under reaction conditions[3] and isomerise to (V).

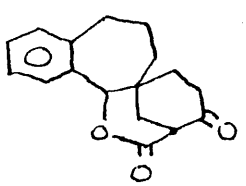
If the above is an equilibrium process then the thermodynamically more stable isomer will be formed and it is possible to predict which will be so, accepting that cycloheptene is a strainless ring system analagous to cyclohexane. Compound (III) contains one cyclo-heptadiene unit and one cycloheptene i.e. equivalent to one cyclohexene and one cyclohexane, whereas (V) the most stable of the products from the alternative reaction

path contains one cyclohexadiene system and one cyclohexane. Since the cyclohexene system is more stable than the cyclohexadiene unit (III) should be the thermodynamically more stable isomer.

The Synthesis of the Ketol (II) (See Sheet VI) P80a

Benzsuberone (I) condensed readily with two moles of acrylonitrile in tert-butanol with Triton B as catalyst to yield the dinitrile (VIII) which was reduced to the alcohol (IX) by methanolic sodium borohydride. The structure of the alcohol was supported by its hydrolysis to the lactonic acid (X).

Unsuccessful attempts were made to cyclise (IX) by means of the Thorpe reaction[4]. Similarly, no success was encountered in cyclising the methanolysis product of (IX) by the Dieckmann method[4], only lactonic products being isolated. Obviously under the basic conditions of reaction, the ester of the lactonic acid (X) was formed by attack of the benzylic hydroxyl on the side chain. In principle this lactonic ester can still cyclise but the β-keto lactone (XXIII) formed could not



XXIII

enolise towards the carbonyl group, since to do so would contravene Bredt's rule[5]. Generally speaking Dieckmann cyclisations under normal conditions are successful only if the enolate of the β-ketoester product can be formed thus shifting the position of equilibrium to the side of the product and since this cannot occur in the above case no cyclisation ensues.

Dieckmann cyclisation of the ketoester (XI), formed by methanolysis of the nitrile (VIII), went in excellent yield with two moles of sodium methoxide in benzene. The half ester (XIII) was isolated as a minor byproduct. Its structure followed from the identity of its hydrolysis product with the dicarboxylic acid (XIV) obtained from the ketoester (XI). This is undoubtedly due to contamination of the sodium methoxide, used in the cyclisation, with water, but the isolation of only the half ester and not the dicarboxylic acid (XIV) suggests that the hydroxide ion is attacking the β-ketoester (XII) and not the starting material (XI).

Now we were faced with the problem of effecting a selective reduction of the carbonyl group conjugate with the aromatic ring. Our first effort in this

direction involved formation of the enol acetate (XV) but its borohydride reduction yielded no useful product.

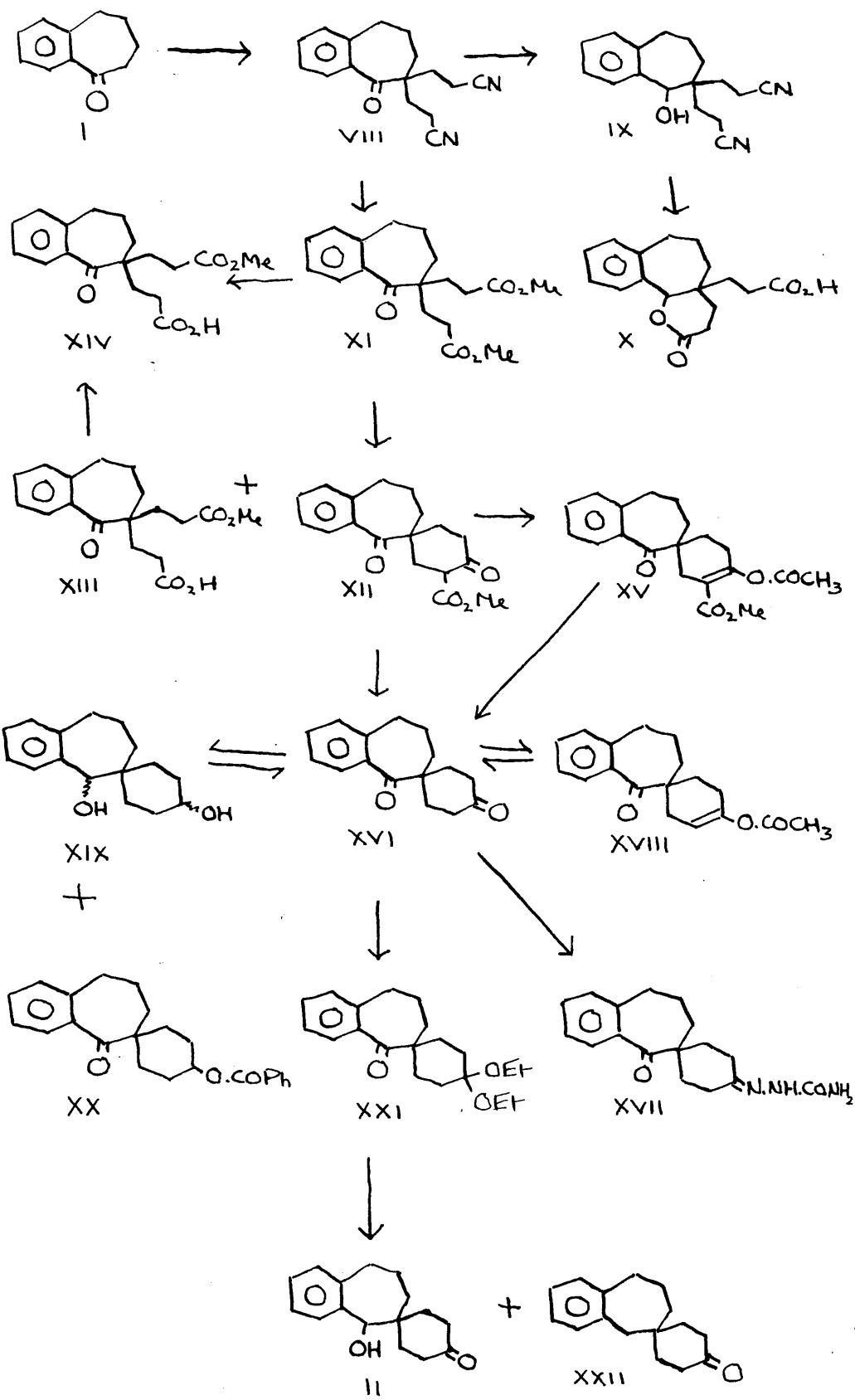
Acidic, or better, basic hydrolysis of the β-keto-ester (XII) gave the dione (XVI) which was also obtained from the enol acetate (XV) thus confirming the structure of the latter. The dione (XVI) absorbed in the infra red at 1710 and 1675 cm^{-1}. demonstrating the different character of the two carbonyl groups. It gave a mono-semicarbazone (XVII) which had a band at 1675 cm^{-1} in the infra red showing that the alicyclic, not the aromatic, carbonyl group had reacted. Borohydride reduction of the semicarbazone (XVII) yielded amorphous products as did similar reduction of the enol acetate (XVIII) formed by reaction of the dione (XVI) with acetic anhydride and p-toluene-sulphonic acid.

The resistance of the diester (XI) to catalytic hydrogenation led us to believe that we could selectively hydrogenate the dione (XVI) but the main crystalline product was the diol (XIX), also obtained from borohydride reduction of the dione (XVI). From the mother liquors, after benzoylation, the keto-benzoate (XX) was obtained in poor yield; that it is not the isomeric compound follows from its infra red band at 1675 cm^{-1} indicating

that the carbonyl group is conjugated to the benzene ring. Some efforts to selectively oxidize the diol (XIX) to the ketol (II) with chromium trioxide in acetic acid or aluminium tert-butoxide and acetone in benzene lead to the dione (XVI) as the only pure isolable compound.

With the failure of the previous methods it was now decided to try ketalisation as a method for the selective protection of the alicyclic carbonyl group. With ethylene glycol and p-toluene-sulphonic acid no selective ketalisation was possible but reaction of the dione (XVI) with ethyl ortho-formate and p-toluenesulphonic acid yielded the ketal (XXI) - CO band at 1675 cm^{-1} but no absorption at 1710 cm^{-1} - which was reduced with boro-hydride or, better, with lithium aluminium hydride in ether to give, after acidic hydrolysis, the ketol (II) whose infra red spectrum showed the expected hydroxyl and carbonyl (1710 cm^{-1}) peaks. Its ultra violet spectrum (see Table IV p 84a) was also consistent with this structure. A byproduct from the lithium aluminium hydride reduction was shown to be the hydrogenolysed ketone (XXII) characterised as its 2:4-dinitrophenylhydrazone.

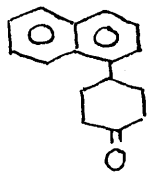
SHEET VI


I
VIII
CN
CN
IX
OH
CN
CN
XIV
CO2Me
CO2H
XI
CO2Me
CO2Me
X
CO2H
XIII
CO2Me
CO2H
+
XII
CO2Me
XV
O.COCH3
CO2Me
XIX
OH
OH
+
XVI
XVIII
O.COCH3
XX
O.COPh
XXI
OEt
OEt
XVII
N.NH.CONH2
11
OH
+
XXII

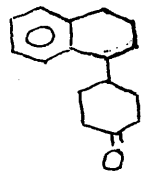
Rearrangement of the Ketol (II)

Of the various reagents used for the rearrangement of the ketol (II) the most satisfactory have proved to be p-toluenesulphonic acid in refluxing benzene and aluminium chloride in ethylene dichloride.

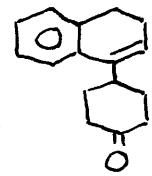
From the latter reaction a ketonic oil was isolated whose ultra violet spectrum, λ_{max}^{EtOH} ($\log \varepsilon$): 273(3.30), 281-282 (3.29) mμ., unequivocally demonstrated that it was an alkyl naphthalene for which (XXIII) is the most obvious structure. As we were unable to prepare crystalline carbonyl derivatives, the ketone (XXIII) was reduced by the Clemmensen method to 1-cyclohexylnaphthalene (XXIV) identified by comparison of its picrate with that of an authentic sample[6]. The hydrocarbon from the rearrangement had, λ_{max}^{EtOH} ($\log \varepsilon$): 273-274 (3.30), 282-283 (3.28) mμ whereas an authentic sample shows[7], log = 3.60. This discrepancy is undoubtedly due to contamination of the naphthalene (XXIV), obtained from the rearrangement, with the tetralin (XXV) since the naphthalene system must be produced initially by disproportionation of the styrene (V) to (XXIII) and (XXVII) by the action of aluminium chloride during the rearrangement.



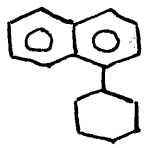
XXIII



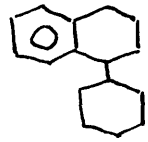
XXVII



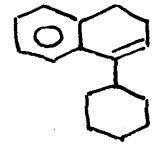
V



XXIV



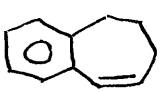
XXV



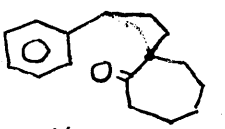
XXVI

In the rearrangement with p-toluenesulphonic acid a gum was obtained. Again we were unable to prepare crystalline derivatives so the ketone was reduced by the Clemmensen method to a hydrocarbon which showed, $\lambda_{max}^{EtOH}(\log\varepsilon)$: 251-254 (3.61) mμ compared to the ketone which had, $\lambda_{max}^{EtOH}(\log\varepsilon)$: 254-255 (3.63) mμ. A pure sample of the dihydronaphthalene (XXVI) synthesised by the method of Cook and Lawrence[6] absorbed at, $\lambda_{max}^{EtOH}(\log\varepsilon)$: 261 (3.98) mμ. suggesting that there was little or none of this hydrocarbon in the reduced product from the

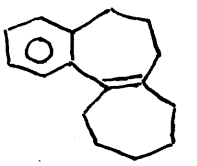
p-toluene-sulphonic acid rearrangement. This was confirmed by comparison of the infra red spectra of the two hydrocarbons. Thus it seems likely that the hydrocarbon from the p-toluene-sulphonic rearrangement product is mainly (XXVIII). This formulation is supported by its ultra violet spectrum since the styrene



XXIX



XXX

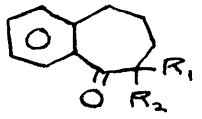


XXVIII

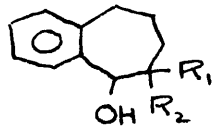
(XXIX) has, λ_{max}^{EtOH} (logϵ): 250 (4.11) mμ. The lowering of the intensity of absorption in (XXVIII) is understandable on the basis of the tetrasubstitution of the double bond since Braude and Sondheimer have shown[8] that similar changes occur in other styrenes due to steric inhibition of resonance. This effect applied to aromatic ketones is effectively demonstrated in the earlier compounds of this series (see Table IV, P 84a).

At present efforts are being made to synthesise (XXVIII) by condensing 3-phenylpropylbromide and cycloheptanone to yield the ketone (XXX) which should cyclise to the desired hydrocarbon.

Table IV



	λ_{max}^{EtOH} (log ε)
$R_1=R_2=H$	246(4.06), 286(3.25)
$R_1=R_2=-CH_2CH_2CN$	246(3.72)
$R_1=R_2=-CH_2CH_2CO_2CH_3$	246(3.88)
$R_1,R_2=-CH_2CH_2COCH_2CH_2-$	244(3.78)



$R_1=R_2=-CH_2CH_2CN$	262(2.36)
$R_1,R_2=-CH_2CH_2CH(OH)CH_2CH_2-$	262(2.43)
$R_1,R_2=-CH_2CH_2COCH_2CH_2-$	262(2.47)

Bibliography

1. e.g. see Gaylord, "Complex Metal Hydride Reductions."
2. Ingold, "Structure and Mechanism in Organic Chemistry," Chapt. IX.
3. Brown, J. Amer. Chem. Soc., 1954, 76, 467.
4. see Gilman, "Organic Chemistry," Vol. I., p. 83.
5. see Chem. Rev., 1950, 47, 219.
6. Cook and Lawrence, J., 1936, 1431.
7. Friedel and Orchin, "Ultra Violet Spectra of Aromatic Compounds," No. 198.
8. J., 1955, 3773.

Experimental

Cyanoethylation of Benzsuberone (1):- Acrylonitrile (20 ml.) was slowly added to a solution of benzsuberone (10 g.) in tert-butanol (50 ml.) containing Triton B (1 ml.). After refluxing the solution for 2 hr., dilution and extraction with ethyl acetate yielded the dinitrile (VIII) (13 g.), m.p. 88-9° from ethanol. (Found: C, 77.00; H, 6.91; N, 10.36. $C_{17}H_{18}ON_2$ requires C, 76.66; H, 6.81; N, 10.52%)

Reduction of the dinitrile (3.0 g.) with methanolic sodium borohydride (0.5 g.) yielded the alcohol (IX) (2.7 g.), m.p. 116-8° from benzene. (Found: C, 76.29; H, 7.50; N, 10.20. $C_{17}H_{20}ON_2$ requires C, 76.08; H, 7.51; N, 10.44%).

Alkaline hydrolysis of the alcohol (IX) gave a small yield of the lactone (X), m.p. 200-1° from ethyl acetate. (Found: C, 70.56; H, 6.70. $C_{17}H_{20}O_4$ requires C, 70.81; H, 6.99%).

Methanolysis of the Dinitrile (VIII):- The ketonitrile (VIII) (10 g.) in methanol (100 ml.) was saturated with dry hydrogen chloride and refluxed for 3 hr. Dilution and extraction yielded the diester (XI) (12 g.), m.p. 72-4° from methanol. (Found: C, 68.74; H, 7.37. $C_{19}H_{24}O_5$ requires C, 68.85; H, 7.28%).

Alkaline hydrolysis of the ester (XI) gave the dicarboxylic acid (XIV), m.p. 175-7° from ethyl acetate. (Found: C, 67.03; H, 6.67. $C_{17}H_{20}O_5$ requires C, 67.09; H, 6.62%).

Dieckmann Cyclisation of the Ester (XI):-

The ester (6 g.) was refluxed for 3 hr. with dry sodium methoxide (from 832 mg. of sodium: 2 moles) in benzene (125 ml.). The reaction mixture was diluted with ethyl acetate and extracted with 5N sodium hydroxide. Concentration of the organic layer yielded the keto-ester (XII) (4.2 g.), m.p. 102-4° from methanol. (Found: C, 71.82; H, 6.44. $C_{18}H_{20}O_4$ requires C, 71.98; H, 6.71%).

Acidification of the alkaline extract yielded the half ester (XIII), m.p. 165-8° from methanol. (Found: C, 67.80; H, 6.91. $C_{18}H_{22}O_5$ requires C, 67.91; H, 6.97%). It was hydrolysed to the dicarboxylic acid (XIV), identical with that previously prepared.

Acetylation of the Keto-Ester (XII):- The keto-ester (500 mg.) was refluxed for 3 hr. with isopropenyl acetate (12 ml.) and p-toluenesulphonic acid (20 mg.). Extraction with ethyl acetate gave the enolacetate (XV) (510 mg.), m.p. 104-5° from petrol. (Found: C, 70.10; H, 6.06. $C_{20}H_{21}O_5$ requires C, 70.36; H, 6.20%).

It was hydrolysed by alkali to the dione (XVI), identical with the sample prepared by hydrolysis and decarboxylation of the ester (XII).

Hydrolysis and Decarboxylation of the Keto-Ester (XII):-

The ester (XII) (2 g.) was refluxed for 2 hr. with potassium hydroxide (3 g.) in water (25 ml.). Extraction with ethyl acetate yielded the dione (XVI) (1.515 g.), m.p. 99-100° from petrol. (Found: C, 79.28; H, 7.56. $C_{16}H_{18}O_2$ requires C, 79.31; H, 7.46%). It gave a mono-semicarbazone (XVII), m.p. 192-5° from ethanol. (Found: C, 68.44; H, 7.03; N, 14.07. $C_{17}H_{21}O_2N_3$ requires C, 68.20; H, 7.07; N, 14.04%).

Acetylation of the Dione (XVI):- A mixture of acetic anhydride (15 ml.), the dione (300 mg.), and p-toluene-sulphonic acid (50mg.) was slowly distilled (ca. 1 hr.) until the volume was reduced to ca. 4 ml.. The residue was taken up in ethyl acetate and shaken with 5N sodium hydroxide. Concentration yielded a dark oil which was filtered through alumina (9 g.) in benzene to yield the enol-acetate (XVIII), m.p. 63-4° from petrol. (Found: C, 76.18; H, 6.95. $C_{18}H_{20}O_3$ requires C, 76.03; H, 7.09%)

Reduction of the Dione (XVI):- (a) After standing overnight a mixture of the dione (XVI) (500 mg.), methanol

(15 ml.), and sodium borohydride (500 mg.) was worked up in the usual way to yield an oily solid which was washed with methanol and crystallised from acetonitrile to give the diol (XIX) (205 mg.), m.p. 214-7°. (Found: C, 77.82; H, 8.70. $C_{16}H_{22}O_2$ requires C, 78.01; H, 9.00%). It gave a dibenzoate, m.p. 166-8° from petrol, (Found: C, 79.59; H, 6.75. $C_{30}H_{30}O_4$ requires C, 79.27; H, 6.65%), which was hydrolysed with methanolic potassium hydroxide to the original diol (XIX).

(b) The dione (XVI) (574mg.) in ethanol (10 ml.) was shaken with Adam's PtO_2 (98 mg.) in the presence of hydrogen until 1 mole had been absorbed. The oil obtained on concentration gave on trituration with methanol the diol (XIX) (54 mg.). Benzoylation of the mother liquors gave, after trituration with petrol-ethyl acetate, the keto-benzoate (XX), m.p. 107-9° from petrol. (Found: C, 79.63; H, 7.21. $C_{23}H_{24}O_3$ requires C, 79.28; H, 6.94%).

Preparation of the Ketol (II):- The dione (XVI) (21 g.) was refluxed for 4 hr. with ethyl ortho-formate (250 ml.) containing p-toluene-sulphonic acid (500 mg.). After diluting with ethyl acetate and washing the solution with 5N sodium bicarbonate, concentration yielded an oil which

was refluxed for 2 hr. with lithium aluminium hydride (5 g.) in ether (250 ml.). After decomposition of the complex the reaction mixture was extracted with ether. Removal of the ether gave an oil which was refluxed for 1 hr. with 1N methanolic hydrochloric acid. Work up of this solution in the usual way yielded an oil which solidified on trituration with petrol to give the ketol (II) (17 g.), m.p. 103-4° from petrol. (Found: C, 78.78; H, 8.23. $C_{16}H_{20}O_2$ requires C, 78.65; H, 8.25%). It gave a 2:4-dinitrophenylhydrazone, m.p. 182-4° from methanol. (Found: C, 62.37; H, 5.53; N, 13.23. $C_{22}H_{24}O_5N_4$ requires C, 62.25; H, 5.70; N, 13.20%).

Distillation of the mother liquors at 160-80° (bath)/0.27 mm. gave the ketone (XXII) which gave a 2:4-dinitrophenylhydrazone, m.p. 157-60° from petrol. (Found: C, 64.55; H, 6.12; N, 13.53. $C_{22}H_{24}O_4N_4$ requires C, 64.66; H, 5.92; N, 13.72%).

Rearrangement of the Ketol (II) (a) After standing for two days a mixture of ketol (II) (2 g.), aluminium chloride (4 g.) and ethylene dichloride (50 ml.) was shaken with water and washed with 10N hydrochloric acid.

Concentration of the organic layer yielded the ketone (XXIII) (1.8 g.) which was reduced by the Clemmensen method to 1-cyclohexylnaphthalene (XXIV), identified as the picrate.

(b) The ketol (500 mg.) was refluxed with p-toluene-sulphonic acid (1 g.) in benzene (40 ml.) for 48 hr. Working up in the usual way yielded a gum (362 mg.) which was reduced by the Clemmenson method to the hydrocarbon (XXVIII).