ALICYCLIC β-DIKETONES

T H E S I S

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by

IAIN MACLEAN

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A C K N O W L E D G E M E N T S

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C O N T E N T S

SUMMARY

(i) The attempted cyclisation of ethyl 13-ketomyristate with potassium t-butoxide at high dilution, gave polymeric material and 13-ketomyristic acid. Ethyl α-acetylbrassylate under similar conditions, and also with sodium hydride as base, gave only ethyl hydrogen α-acetylbrassylate along with polymeric material.

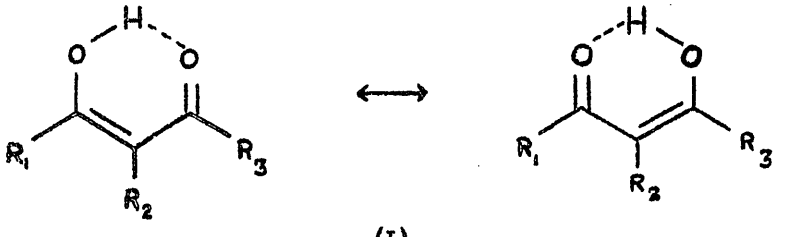
(ii) The cyclisation of ethyl 6-oxo-5-phenylheptanoate with sodium ethoxide was shown to give 6-oxo-5-phenylheptanoic acid, 2-acetyl-5-phenylcyclopentanone and a mixture of 3-ethoxycarbonyl-2-methyl-1-phenylcyclopent-1-ene and 3-ethoxycarbonyl-2-methyl-1-phenylcyclopent-2-ene.

(iii) A route to cycloheptane-1,3-dione by isomerisation of the epoxide of the previously reported 2-oxocyclohexylideneacetic acid failed, and reinforced doubts as to the structure of the starting material. Cycloheptane-1,3-dione was finally synthesised by catalytic hydrogenation of 1,3-dimethoxycycloheptatriene, followed by hydrolysis of the resulting diene with oxalic acid. The instability of a conjugated enone system in a seven-membered ring was demonstrated.

GENERAL INTRODUCTION

Acyclic β-dicarbonyl compounds have been readily accessible from the earliest days of organic chemistry, as indeed have several cyclohexane-1,3-diones. Recent work has shown the dependence of both the physical and the chemical properties of compounds containing this functional group on the steric interactions operating in the molecule.

In a β-dicarbonyl compound, enolisation is encouraged by the resultant formation of a conjugated enone system. Measurement of the enol content of acyclic β-diketones by Meyer[1] by bromine titration, surprisingly showed that in polar solvents they exist to a large extent in the diketo form, while in non-hydroxylic solvents they are extensively enolised. In addition, the enol forms are more volatile than the diketo. To explain these anomalies, Sidgwick[2] introduced the concept of a strain-free enol chelate, in which the enolic proton, simultaneously held by both carbonyl groups, forms a six-membered hydrogen bridged ring of pseudo-aromatic character (I).



(I)

Since the enolic proton is no longer available for intermolecular exchange with the solvent, the enol form is now more hydrophobic than the diketo form. As a consequence, the solubilities of the two forms in a given solvent are once again in agreement with the van't Hoff-Dimroth[3] expression:

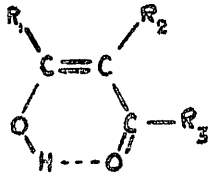
$$\frac{[\text{enol}]}{[\text{keto}]} = G \times \frac{\text{solubility enol}}{\text{solubility keto}}$$

where G is a constant independent of the solvent.

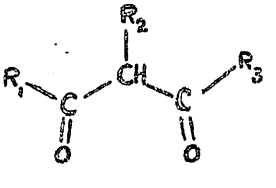
The existence of these enol chelates has since been confirmed by ultraviolet[4] and infrared[5] spectral measurements.

The stability conferred on β-diketones by formation of this hydrogen bonded ring, dictates that the chelate will be the preferred form where steric factors permit, i.e. if the enol of the acyclic β-diketone can be planar (to maximise resonance energy) and cyclic (to permit strong hydrogen bond formation).

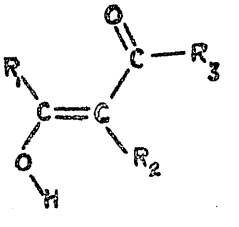
Open chain β-diketones are in fact an equilibrium mixture of three forms, namely the diketo, the cis-enol, and the trans-enol. In any solvent the equilibrium depends on the ionisation constants of these forms, i.e. their acidic properties and degree of solvation.



cis-enol



diketo



trans-enol

While conducting an examination of the colours of the iron complexes produced when β-diketones are treated with aqueous or methanolic ferric chloride, Henecka[6] observed several β-diketones which gave no colouration, but which could be shown by bromine titration to contain appreciable amounts of the enolic form. This was especially true of compounds containing a branched α-substituent such as isopropyl. He attributed the absence of complex formation to steric prevention of cis-enolisation, causing exclusive formation of the trans-enol. A similar postulate had previously been used by Arndt et al.[7] to explain (incorrectly) the apparently anomalous solubility properties of keto-enol systems.

In acyclic β-diketones it is only on enolisation that the bulk of the alkyl substituents becomes vitally important, and can affect the formation of the enol chelate. In the diketo form, where there is free rotation about the carbon-carbon single bonds, the size of the substituents has little influence on conformation. The trans-conformation is favoured by low dipole moments as one would expect the value for the cis-isomer to be high.

The idea of 'trans-fixed' β-dicarbonyl compounds has been developed with special reference to the alicyclic series by Eistert and Reiss.[8] When a β-dicarbonyl function is contained in a four-, five-, or six-membered ring, not only are the carbonyl groups held in a trans alignment in the diketo form, but

cis-enolisation is sterically impossible so that chelate formation cannot occur.

In a study of β-diketones in solution, Kabachnik and his co-workers[9] applied the theory of acid-base equilibrium to the tautomeric equilibrium between the ketonic and cis- and trans-enolic forms of β-diketones. That the tautomeric equilibrium is ionic, involving proton transfer, and is determined by the equilibrium of keto and enol forms with their corresponding anions and solvated protons, was verified experimentally,[10] i.e.

$$KH + S \rightleftharpoons E^- + SH^+ \rightleftharpoons EH + S$$

where KH is the diketo form, EH is the enol form and E^- the enolate anion of a β-diketone, and S is the solvent.

It was found that 'trans-fixed' β-diketones did not obey the relationship developed by Meyer[1] for keto-enol equilibrium constants:-

$$K = EL$$

where E is a constant measuring the enolisability of the solute and L is a constant measuring the enolising power of the solvent. This is explained by the fact that cis- and trans- enols are acids of different chemical types, while the Meyer expression is developed from the Brønsted[11] theory of acid-base equilibrium which considers acids of the same type. As a result two distinct equations must be considered, one for the keto cis-enol equilibrium and one for the keto trans-enol equilibrium:-

$K_{\underline{cis}\text{-enol/keto}} = EL$ and $K_{\underline{trans}\text{-enol/keto}} = E'L'$

Where E and E' are constants which measure the tendency of the solute to enolise to the *cis*- and *trans*- enol respectively, and L and L' are constants denoting the enolising capacity of the solvent to the *cis*- and *trans*- enol respectively. E and E' are independent of the solvent, and are determined by the structure of the keto-enol, while L and L' depend solely on the solvent and are common to all keto-enols.

The overall equilibrium constant, which is that measured by bromine titration, is now expressed by

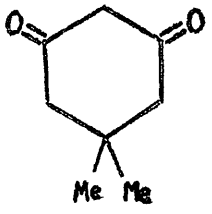
$$K = EL + E'L'$$

Results obtained by Kabachnik[9] for the enol contents of certain '*trans*-fixed' β-diketones, led him to believe that *trans*-enolisation was independent of solvent (i.e. $K = EL + E'$), but this was refuted by Eistert and Geiss[12] for '*trans*-fixed' β-diketones of the dimedone type and cyclic malonic esters. More recent work by Eistert and Geiss[13] and by Kabachnik and his co-workers,[14] has led to the further subdivision of '*trans*-fixed' β-diketones into three categories:-

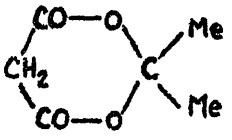
(i) Cyclic β-diketones of the dimedone type (II) whose *trans*-enolisation is solvent dependent, being enhanced in hydrophilic solvents.

(ii) Cyclic acylals of malonic ester, such as isopropylidene malonate (III) (Meldrum's Acid), which are completely unenolised and in which equilibrium takes place directly between the diketo form and the enolate anion. Here, addition of a proton to the cyclic anion does not cause any gain in mobility, so that the anion has a low proton affinity and these compounds are therefore highly acidic.

(iii) α-Akyltetronic acids (IV), α-alkylacetoacetic esters and α-alkylacetylacetonates whose trans-enolisation is apparently independent of solvent. In fact it does vary with solvent, but the changes in solvation energy of ketonic and trans-enolic forms with solvent are so small that trans-enolisation is constant to a first approximation.



(II)



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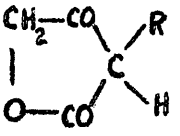
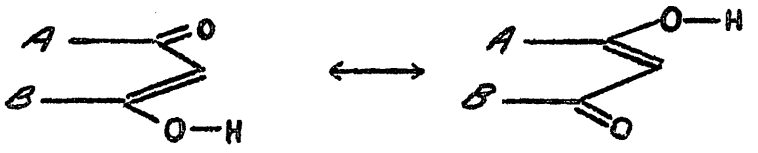


(IV)

All further considerations will be concerned solely with the first of these categories.

'Trans-fixed' β-diketones owe their distinctive properties to the inability of their enols to chelate. In four-, five-, and six-membered rings, the diketo form of β-diketones is a

rigid structure. Enolisation, therefore, occurs readily, as the increase in rigidity resulting from formation of the enone system (V) is small, and gives rise to the trans-coplanar arrangement in which oxygen-oxygen repulsion is minimised and resonance stability is maximised.



(V)

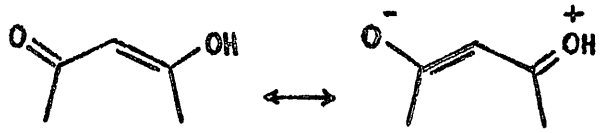
(The enols of acyclic β-diketones are less stable in this conformation, as there is interference between the residues A and B flanking the functional group).

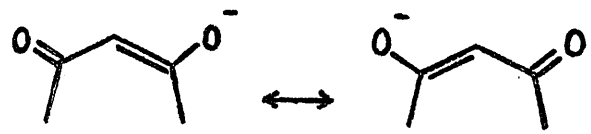
Trans-enolisation is encouraged by intermolecular hydrogen bonding. As a result, enolisation in non-polar solvents is concentration dependent, and falls with increased dilution. The trans-enol has a proton available for hydrogen bonding to a molecule of solvent, and its formation is therefore enhanced in hydroxylic solvents. Conversely enolisation is inhibited in non-polar solvents.

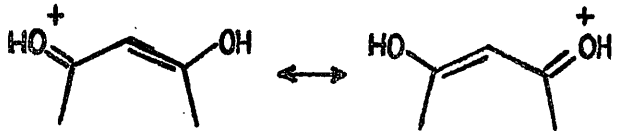
Eistert and co-workers[15] observed the high acidity of these cyclic β-diketones, which have pK_a values typically in the

range 2.8-5.5. α-Monosubstitution of the β-dicarbonyl function diminishes this acidity, while it is of course completely absent in the non-enolisable αα-disubstituted compounds. The acid strength of unsubstituted '*trans*-fixed' β-diketones results from their extensive enolisation, and from the gain in resonance energy obtained by formation of a symmetrical resonance stabilised anion (VI). Removal of the proton does not involve the breaking of a hydrogen bond as it does in chelated *cis*-enols. The rigidity of the enolate anion so produced is even greater than that of the enol, but since the original diketo form is itself rigid, there is no great entropy change due to loss of mobility. Blout *et al.*[16] have shown that the extent of enolate anion formation of cyclic β-diketones in neutral solution is concentration dependent, and increases with dilution.

'*Trans*-fixed' β-dicarbonyl compounds exhibit amphoteric halochroism.[15b] In going from neutral to alkaline solution, there is a bathochromic shift in the ultraviolet absorption maximum of about 250-300Å, due to the conversion of the unsymmetrical enol (V) to the symmetrical, resonance stabilised, enolate anion (VI). In concentrated acid, a slightly smaller bathochromic shift is observed due to formation of the symmetrical oxonium cation (VII). In both cases the extinction coefficient is increased, to a greater extent for the enolate anion.

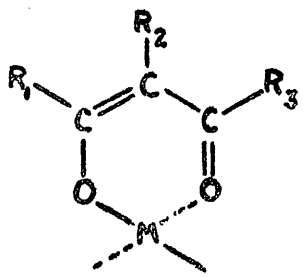
(V)  enol (unsym.)

(VI)  enolate anion (sym.)

(VII)  oxonium cation (sym.)

The chemical properties of β-diketones are also influenced by '<u>trans</u>-fixing'. The enol ethers of '<u>trans</u>-fixed' β-diketones[8] are much more readily prepared than those of the acyclic series, where formation of the ether involves breakage of the enol chelate ring.[17]

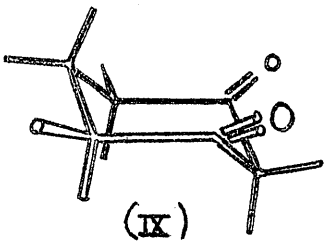
The formation of copper complexes by shaking with copper acetate, or indeed of the complexes of any bivalent metals (VIII) as found with <u>cis</u>-enolisable analogues,[18] is sterically impossible with '<u>trans</u>-fixed' β-diketones. Cyclic β-diketones can however



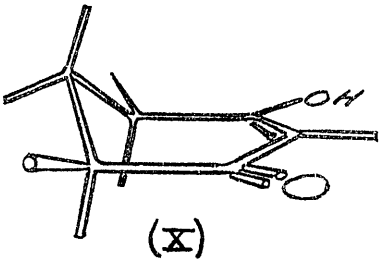
(VIII)

form salts with metals and care is required not to misinterpret this phenomenon as evidence of the formation of coloured complexes. Thus dimedone can be induced to give a colour with methanolic ferric chloride.

In cyclic β-diketones '<u>trans</u>-fixing' is a function of ring size. While in four- and five-membered rings the two carbonyl groups are held <u>trans</u>-coplanar, in the diketo form of cyclohexane-1,3-dione (IX) the carbonyl groups, though still rigidly held, are skew to one another. The enone (X) once again provides a



(IX)



(X)

<u>trans</u>- coplanar system.

As the ring size is enlarged, the factors keeping the oxygen atoms apart will be reduced and an increase in the mobility of the molecule will become apparent. Models of the seven-membered cyclic β-diketone show the diketo form to have a considerable degree of freedom. As with the six-membered ring, the conformation with <u>trans</u>-coplanar carbonyl groups is unstable, involving in this case a strong 1,4-transannular interaction and eclipsed methylene groups (see Section III). On enolisation,

these steric factors are again present in the trans-coplanar conformation, and a non-coplanar conformation, in which the advantages of conjugation are minimised, is more favoured.

If the number of carbon atoms in the ring is progressively increased, a sufficiently large ring size should be reached at which the properties of the alicyclic β-diketones revert to those of the open chain series, with the possibility of cis-enolisation and chelation. Increasing the ring size in other series has caused similar reductions in strain, e.g. in cyclo-octene it has been shown that the conformation with a trans-double bond is capable of existence,[19] and exceptions to Bredt's rule[20] are frequent in the macrocyclic series.[21] An examination of the relationship between the 'trans-fixing' of alicyclic β-diketones and ring size is therefore desirable. Unfortunately, it is probable that reversion to acyclic properties will only be found in very large rings, and a study of the problem has been hampered by the inaccessibility of these macrocyclic β-diketones.

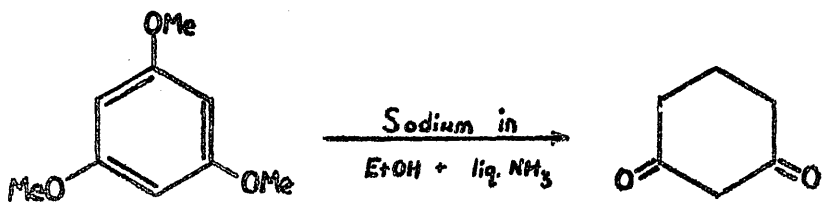
While cyclohexane-1,3-dione has long been available by Dieckmann cyclisation of ethyl 5-oxohexanoate[22] (XI) and of ethyl 2-ethoxycarbonyl-5-oxohexanoate[23] (XII) or, more usefully, by catalytic hydrogenation of resorcinol using a variety of catalysts,[24] these methods cannot be extended to macrocyclic β-diketones.

$CH_3CO(CH_2)_3COOEt$ (XI)

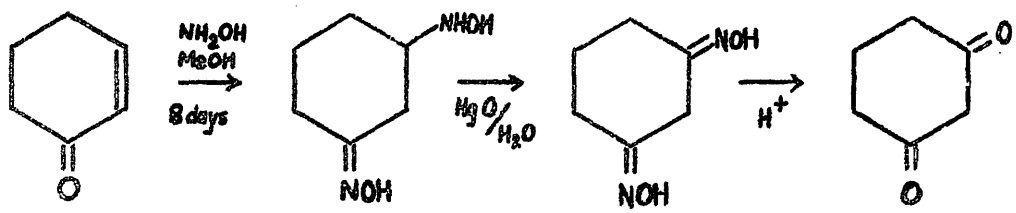
$CH_3CO(CH_2)_2CH(COOEt)_2$ (XII)

Other routes to this dione are:-

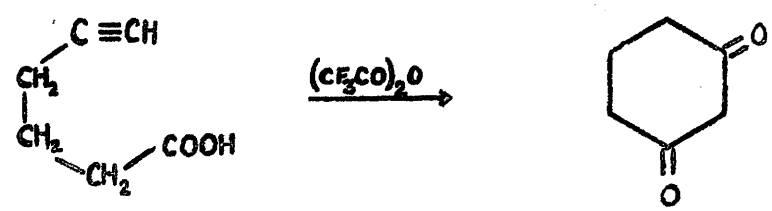
(1) Birch reduction of 1,3,5-trimethoxybenzene,[25]



(2) the synthesis of Kötz and Grethe,[26] by formation of the dioxime from cyclohexenone and subsequent hydrolysis,

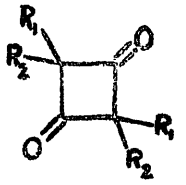


(3) cyclisation of ω-hexynoic acid with trifluoroacetic anhydride,[27]



The last two preparations suggest possible synthetic paths to β-diketones of higher ring size, although negative results are reported[27] in an attempted cyclisation of ω-heptynoic acid.

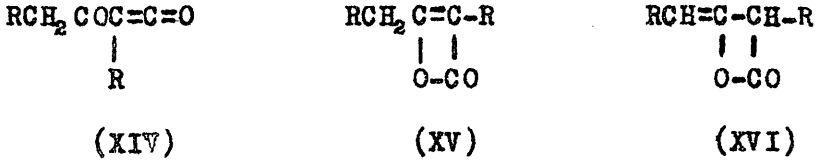
In the four-membered ring series, tetra-alkylcyclobutane-1,3-diones (XIII) are easily obtainable by symmetrical dimerisation of ketoketenes.[28] The structure of these dimers has been confirmed



(XIII)

by Raman spectra,[29] X-rays,[30] and electron diffraction.[31]

Aldoketenes and ketene itself can theoretically dimerise to give any of five products, viz.



(XIV) (XV) (XVI)

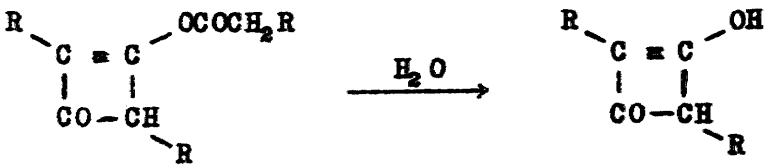
(XVII) (XVIII)

Since the claim by Chick and Wilsmore,[32] based on a suggestion by Staudinger and Bereza,[33] that the product they obtained on dimerisation of ketene was cyclobutane-1,3-dione (XVII, R = H), controversy has raged as to the true nature of

this dimer. As recently as 1943, Rice and Roberts[34] still preferred this formulation. The accumulation of evidence which has led to the acceptance of the vinyl-lactone (XVI, R = H) as the true structure is well summarised in a recent paper by Enk and Spes,[35] the most weighty being electron diffraction measurements.[36]

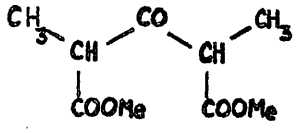
As with ketene, the dimers of aldoketenes are so reactive that determination of the correct structure by the methods of organic chemistry is difficult. Dimerisation of methylketene gave two forms - a liquid with similar properties to diketene and accepted as having a β-lactone structure,[37] and a crystalline acidic form which Woodward and Small[38] have identified as the enol (XVIII, R = Me).

Enk and Spes[35] have also shown that the trimers of aldoketenes are enol esters of dialkylcyclobutane-1,3-diones (XIX) from which the free enols (XVIII) are readily obtained by hydrolysis.



(XIX) (XVIII)

An earlier claim[39] to the preparation of 2,4-dimethylcyclobutane-1,3-dione by cyclisation of dimethyl αα'-dimethylacetonedicarboxylate (XX) with cold sulphuric acid followed by saponification and decarboxylation, was shown[38,40] to furnish instead, the pyranone (XXI). On treatment with barium hydroxide,



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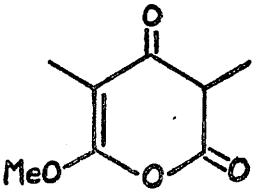
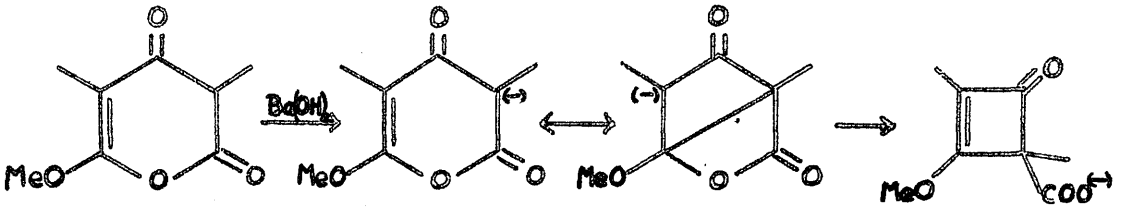


(XXI)

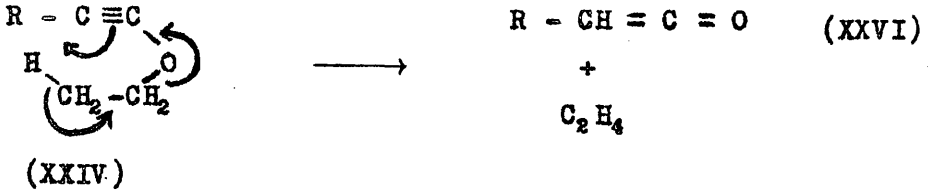
however, this product rearranges to give 2,4-dimethylcyclobutane-1,3-dione (XVII, R = Me) and provides the most useful source of this compound. The mechanism which Woodward[38] has postulated for the rearrangement involves ionic intermediates (XXII) and (XXIII).



(XVII) (XXIII)

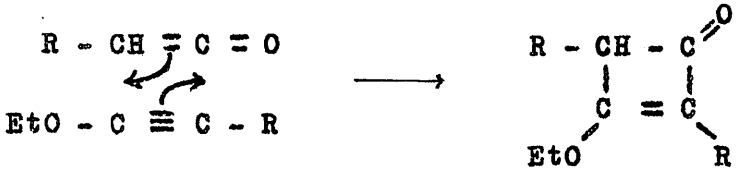
The preparation of cyclobutane-1,3-dione itself has now been realised by Wasserman and Dehmlow.[41] Nieuwenhuis and Arens[42] had shown that pyrolysis of ethynyl ethers (XXIV) gave cyclobutane-1,3-dione enol ethers (XXV), and suggested a mechanism which

involved initial ketene formation followed by reaction with a further molecule of the ether. The practical soundness of this



(XXIV)

(XXVI)

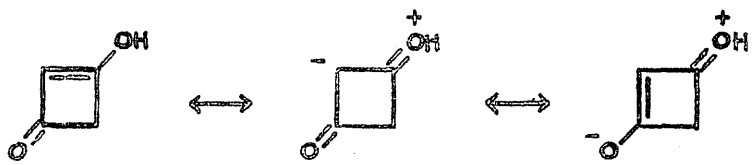


(XXV)

mechanism was confirmed in reactions between ketenes and 1-alkoxy-1-alkynes (XXIV),[43] which gave rise to monoalkylcyclobutane-1,3-diones.

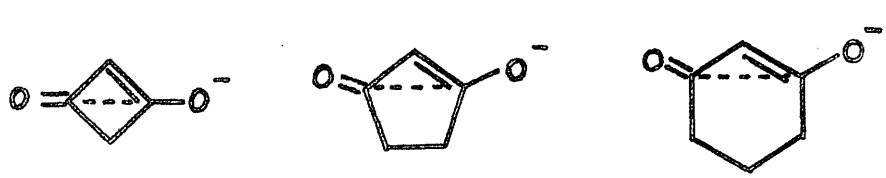
Wasserman and Dehmlow[41] found that by bubbling ketene (XXVI, R = H) through ethoxyacetylene (XXIV, R = H) in methylene chloride and hydrolysing the enol ether formed with cold sulphuric acid, cyclobutane-1,3-dione (XVII, R = H) was readily available in 30% yield. The diketone is solid, stable at low temperatures, and exhibits infrared absorption both in the solid state and in chloroform solution consistent with a four-membered ring ketone, and extremely weak double bond absorption (Table I). The nuclear magnetic resonance spectrum in deuterochloroform shows that it exists exclusively as the dione in this solvent,

while in polar media it is largely unenolised. Also in keeping with its 'trans-fixed' structure is a pK_a value of 3. This exceptional acidity is in agreement with previous predictions. Woodward and Small[38] had attributed the high acidity of 2,4-dimethylcyclobutane-1,3-dione to the fact that in the ground state a greater contribution by the forms (XXVII) and (XXVIII) would be expected, especially (XXVII) as this removes the double bond from the ring and thereby reduces ring strain. Roberts and his co-workers[44] preferred to explain the acidity by

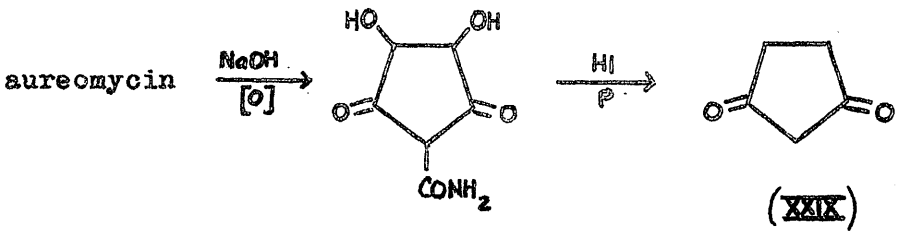


(XXVII) (XXVIII)

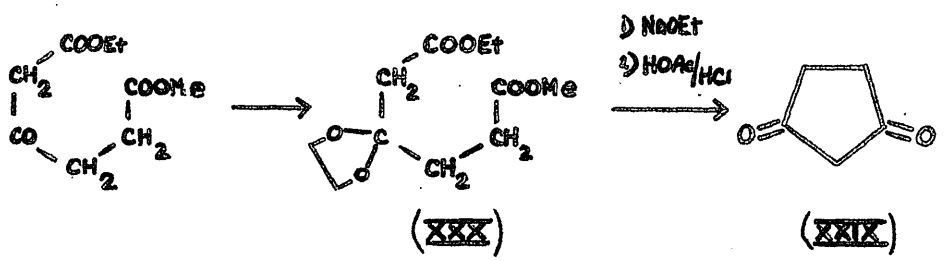
considering the increase in delocalisation due to cross-ring, non-bonded, electronic interaction. For the cyclane-1,3-diones the delocalisation energies calculated from L.C.A.O. theory diminish as ring size is increased from four to five to six, and hence the anion becomes less stable as the ring is enlarged.



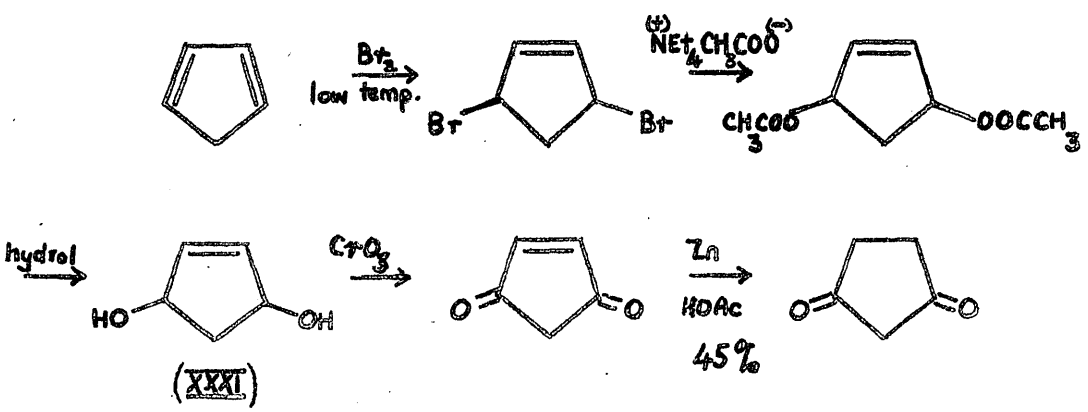
In the five-membered ring, the parent dione has again proved more inaccessible than its derivatives. Cyclopentane-1,3-dione (XXIX)[45] was first obtained as a degradation product of aureomycin.



The synthetic dione was prepared by Boothe et al.[46], in an overall yield of 7.5%, by cyclising the ethylene ketal of ethyl methyl β-ketoadipate (XXX) followed by hydrolysis and decarboxylation.



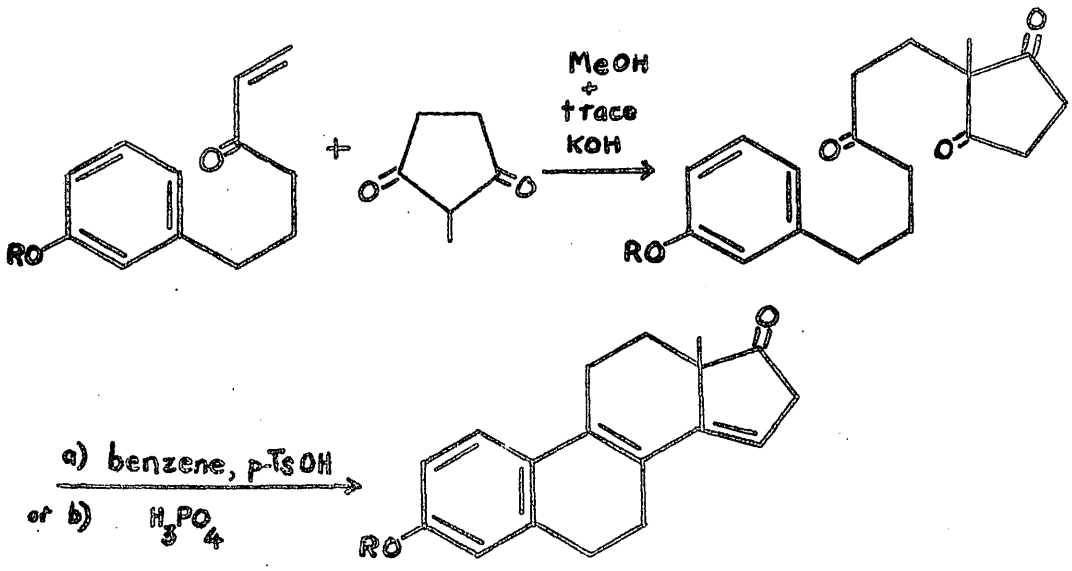
Depuy and Zaweski[47] have also obtained cyclopentane-1,3-dione by the following route from cyclopentadiene:-



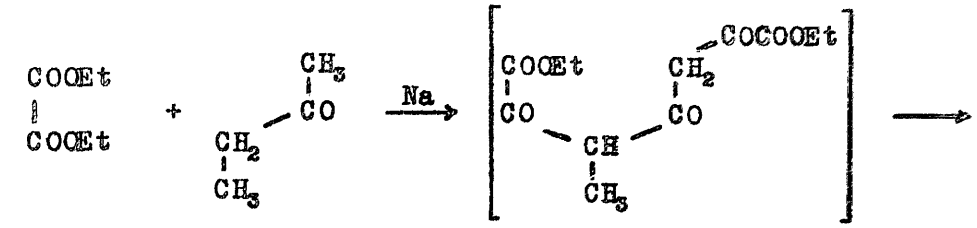
Alte[illegible] conducted using either palladium,[48] or Raney nickel with a trace cond[illegible] of potassium iodide.[49] As cyclopentene-3,5-diol (XXXI) is now commercially available, cyclopentane-1,3-dione has been rendered readily accessible.

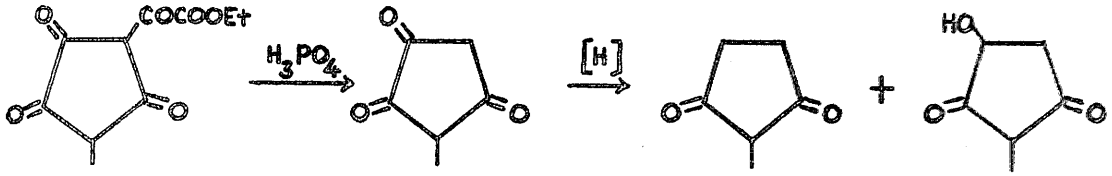
The five-membered dione is a white solid whose infrared absorption (Table I) indicates partial enolisation. The ultraviolet absorption in acid at 2420 Å.(ε 20,700) undergoes a bathochromic shift in alkali to 2570 Å.(ε 29,400). As expected, it has a somewhat lower acidity than cyclobutane-1,3-dione (Table I) and gives no coloured complex with ferric chloride.

The 2-methyl derivative of cyclopentane-1,3-dione is worthy of mention because of its extensive use in the total syntheses of steroids[115] to provide a D-ring having a 17-oxo function, e.g.



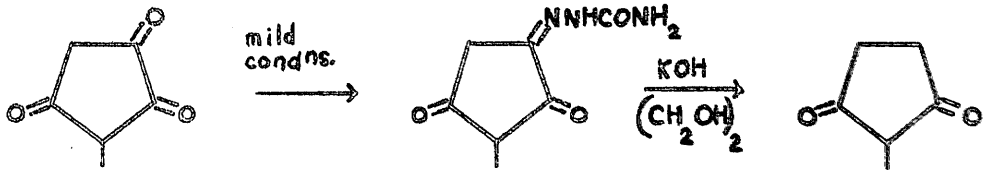
Orchin and Butz[116] prepared 2-methylcyclopentane-1,3-dione from methyl ethyl ketone and ethyl oxalate as follows:-





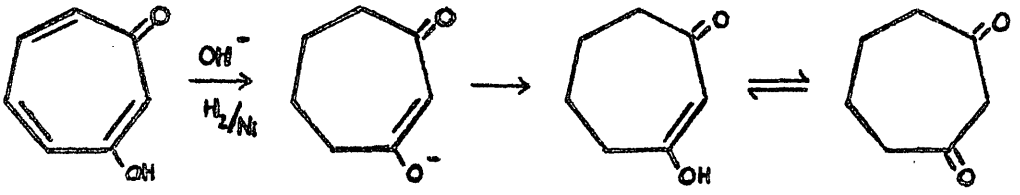
(XXXII)

In the reduction stage a mixture was obtained which contained the desired ketone in poor yield. Panouse and Sannié[117] found that a modified final stage, in which the monosemicarbazone of the trione (XXXII) was reduced under Wolff-Kishner conditions, gave 2-methylcyclopentane-1,3-dione in 86% yield.



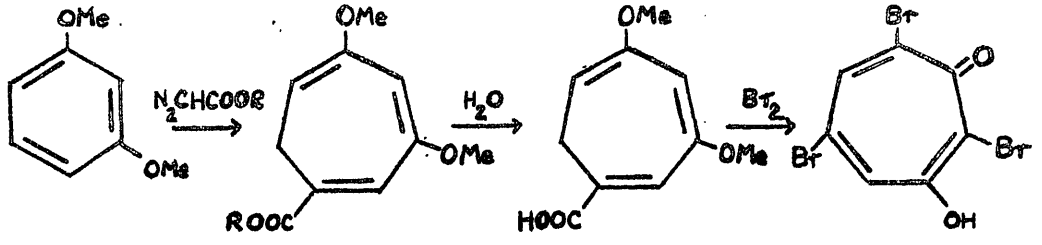
Of the cyclic β-diketones with more than six ring members the only parent compound reported till now was cycloheptane-1,3-dione (XXXIII), details of which were published during the course of our own investigations. This compound was first prepared by Eistert, Haupter and Schank,[50] who used the

catalytic hydrogenation technique of Klingenfuss[51] to reduce β-tropolone (XXXIV) to the enolate anion of cycloheptane-1,3-dione.



(XXXIV) (XXXIII)

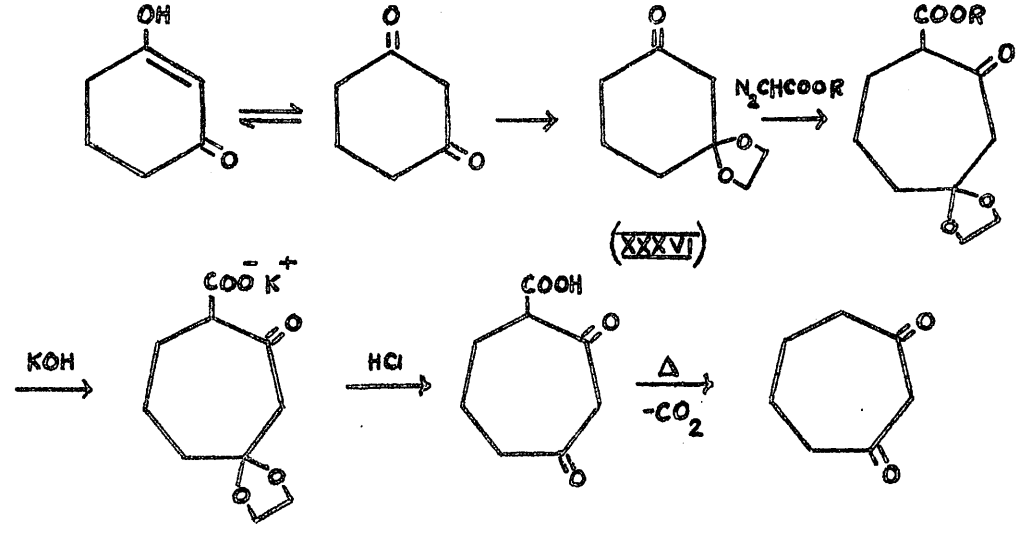
As β-tropolone is itself obtained by catalytic hydrogenation of 2,5,7-tribromo-3-hydroxytropone (XXXV), Raney nickel hydrogenation of this compound under basic conditions gave the enolate anion, and by acidification the free dione. The tribromo-compound was obtained from resorcinol dimethyl ether by the route[52] outlined below.



(XXXV)

The yield of cycloheptane-1,3-dione obtained by this hydrogenation technique was only 4%.

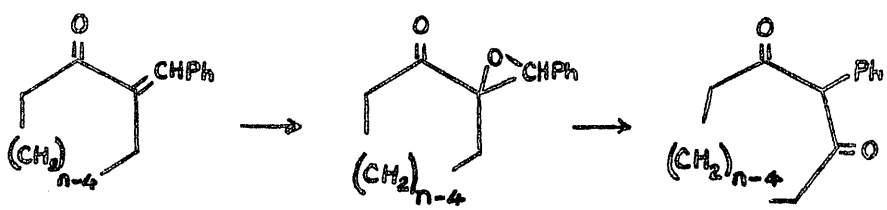
After many unsuccessful attempts to improve this yield by ring closure and expansion techniques, the same authors[63] obtained cycloheptane-1,3-dione by ring expansion of the mono-ketal of cyclohexane-1,3-dione (XXXVI) with diazoacetic ester using zinc chloride as catalyst. The ester produced was hydrolysed with base, as acid hydrolysis caused ring opening. Acidification to rupture the ketal followed by thermal decarboxylation gave cycloheptane-1,3-dione, which could be extracted with ether only after the aqueous solution had been saturated with ammonium sulphate.



By adherence to rigidly defined experimental conditions, an overall yield of 28% based on cyclohexane-1,3-dione was obtained. The product was found to be an oil, and behaved to

some extent as a 'trans-fixed' β-diketone giving no ferric chloride colouration and no metal chelates.*

An apparently general method for preparing 2-phenylcyclane-1,3-diones (XXXVII) has been reported by House and Wasson,[54] who epoxidised mono-α-benzylidenecyclanones (XXXVIII) and rearranged the epoxide with boron trifluoride. In this way the six-, seven-, and eight-membered ring compounds were prepared (see Table II).



(XXXVIII) (XXXVII)

The properties of the six-membered ring analogue again indicate an enolised structure, while the seven- and eight- exist largely in the diketo form. Lack of enolisation in these cases was attributed to steric factors, which inhibit formation of a planar conjugated enone system in rings of this size.

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* Details of the properties of cycloheptane-1,3-dione are given in Section III.

TABLE I

Dione	Phase	I.R. ($cm.^{-1}$)		U.V. (Å)		pK_a
		mull or film	$CHCl_3$	neutral*	+trace OH^-	
cyclobutane-1,3-dione	solid (m.p.119-120°)	1755 (s) 1570 (w)	1755 1570 (v.w.)	2370 (11,800)		~3
cyclopentane-1,3-dione	solid (m.p. 150-151°)	1717 1649 1562	1703 1668 1589	2420 (20,700) [in 0.1N HCl]	2570 (29,400) [0.1N NaOH]	4.5
cyclohexane-1,3-dione	solid (m.p.105-106°)		1741 1717	2550 (22,300)	2800 (26,650)	5.1
cycloheptane-1,3-dione	liquid (b.p. 119-121°/15mm)	1728 1704		2650 (3,410) (transparent in CCl_4)	2880 (24,060)	8.64
acetylactone	liquid (b.p. 139°)	1730-1700 1650 1600	1709 1639-1538 (b)	2720 (12,500)	2930 (21,900)	9

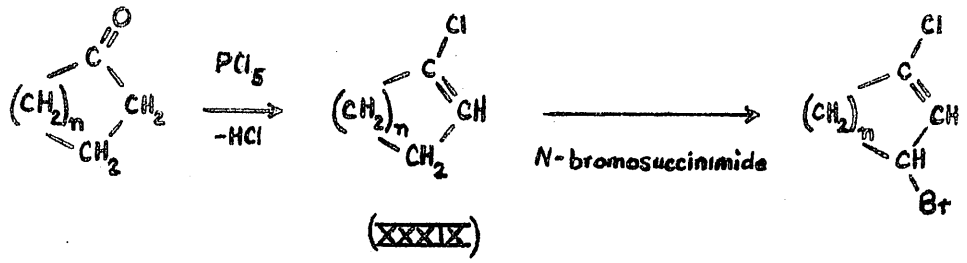
*Solution in ethanol unless otherwise stated.

TABLE II

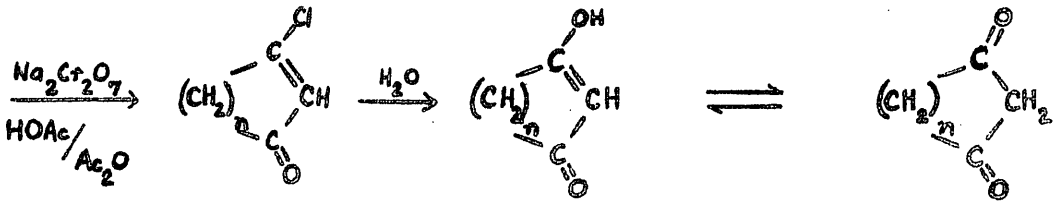
Dione XXXVII	Phase	Ferric Chloride (aq.)	I.R. ($cm.^{-1}$)	U.V. (Å)
n = 5	plates (160-161°)	+ve violet	3400 (unassoc. COOH) 3000 (assoc. COOH) 1615 (broad, enolised dione) 1590	2650 (9300) 2300-2570 (6200)
n = 6	needles (76-77°)	-ve	no OH 1720, 1695 (unenolised dione)	2660 (3100)
n = 7	plates (43-45°)	-ve	no OH 1705, 1680 (unenolised dione)	2590 (673) 2650 (643)

The dependence of the properties of cyclic β-diketones on ring size is demonstrated in Table I, in which the properties of the four-, five-, six- and seven-membered ring compounds are compared with those of acetylacetone.

While certain special macrocyclic β-diketones have been prepared,[55] large ring compounds with this functional group have been virtually undocumented and the problem of relating ring size to the properties of the β-dicarbonyl function has been neglected. Since the preparation of this manuscript, however, a general synthetic route to cyclic β-diketones has been reported in a preliminary publication by Eistert and Schank.[118] These authors converted alicyclic ketones to 1-chlorocyclenes (XXXIX) by halogenation with phosphorus pentachloride and subsequent dehydrochlorination. Allylic bromination and oxidation with sodium dichromate then gave the 3-chlorocyclenones (XL), which on hydrolysis gave the cyclic β-diketones (XLI). In this way cyclo-octane-1,3-dione (XLI, n = 5) cyclononane-1,3-dione (XLI, n = 6) and cyclo-dodecane-1,3-dione (XLI, n = 9) were prepared. While the



(XXXIX)



(XL) (XLI)

eight- and nine-membered ring compounds showed a very weak tendency to enolise similar to cycloheptane-1,3-dione, the twelve-membered analogue had lost all '<u>trans</u>-fixed' nature and behaved like acetylacetone. Cyclododecane-1,3-dione crystallised as the enol chelate, and was more strongly enolised in hydrophobic solvents than in neutral hydroxylic solvents. It gave a red complex with ferric chloride and formed a copper chelate. In contrast to the eight- and nine-membered cyclic β-diketones which gave crystalline 2,4-dinitrophenylhydrazones, cyclododecane-1,3-dione gave a pyrazole (as does acetylacetone).

The authors are proceeding with the preparation of the other medium ring cyclic β-diketones, in order to examine the transition from '<u>trans</u>-fixed' to <u>cis</u>-enolisable compounds.

S E C T I O N I

HIGH DILUTION CONDENSATIONS

Interest in macrocyclic ketones developed after the proofs of structure of civetone[56] and muscone[57] by Ruzicka, and more recently of products from the scent gland of the musk rat.[58] Because of their odoriferous nature, this interest has expanded in conjunction with the perfume industry.

Synthetic routes to these compounds have been evolved by pyrolysis of transition metal salts of α,ω-diacids,[59] by cyclisations of α,ω-dinitriles,[60] diketenes,[61] and ω-haloacylacetic esters,[62] and by the acyloin process.[63] Even when using the high dilution techniques propounded by Ruggli[64] to prevent intermolecular reaction, preparative yields of medium ring compounds (eight- to twelve-membered) have been negligible except by the acyloin approach. Prelog[65] attributed lack of ring closure in this region to ring strain and van der Waal's repulsion. A recent attempt by Leonard and Schimelpfenig[66] to extend the Dieckmann cyclisation to rings with more than seven carbon atoms, by using potassium t-butoxide in refluxing xylene at high dilution, has confirmed previous impressions. The difficulties encountered in the formation of medium ring compounds have been reviewed by Huisgen.[67]

Until very recently no large ring β-diketones had been prepared. Leonard and Owens,[68] hoping to oxidise the corresponding

β-hydroxyketones, treated αβ-cyclenones* with hydrogen bromide to give the β-bromoketones. All attempts to hydrolyse these gave not the β-hydroxyketone, but a mixture of αβ- and βγ - cyclenones, indicating either that dehydrobromination is faster than replacement or that the β-ketoalcohols are too unstable to be isolated. Oxidation of 3-(1'-pyrrolidino)-cyclotetradecanone with a variety of reagents chosen to prevent ring fission, and of the enol acetate of cyclodecanone with selenium dioxide, also failed.

The difficulties occasioned in the preparation of medium-sized cyclanones by the steric requirements of ring formation and by the instability of the products, will be further increased by the presence of a second carbonyl function. Acyclic β-diketones are obtained from methyl or α-methylene ketones by acylation, either with esters and acid chlorides in the presence of basic condensing agents or with anhydrides in the presence of acidic condensing agents.[69] More recently they have been prepared by the acylation of enamines.[70] It was thought that adaptation of the base catalysed acylations of ketones to produce intra-molecular condensations in compounds with long carbon chains would be feasible using high dilution techniques.

The requirments, as summarised by Henecka,[71] for this type of condensation are 1) a strongly acidic methylene component

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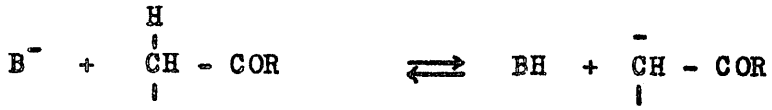
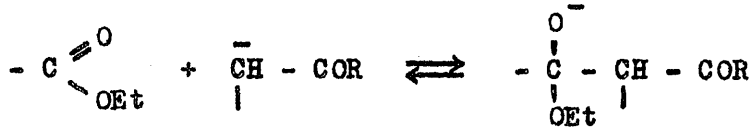
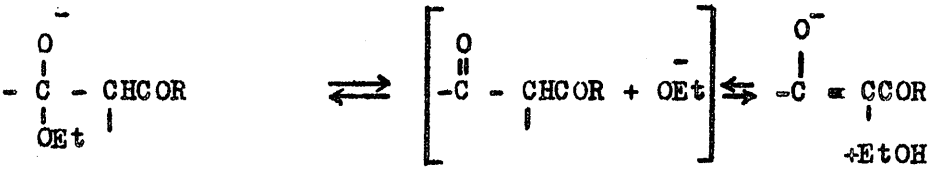
*Ultraviolet data quoted leave some doubt as to the purity of these isomers.

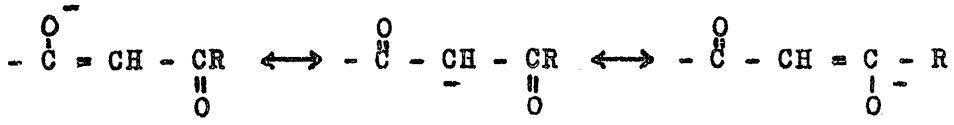
2) a readily polarisable carbonyl function, and 3) the production of a resonance stabilised anion which will displace the equilibrium in favour of the condensed product. The condensation may be considered to occur in three reversible stages:-







The product is resonance stabilised as follows:-



The reaction is dependent on equilibria in a polar medium and thus, in base, the strongest possible acid will be produced. Henecka explained the reluctance of Dieckmann cyclisations to produce large rings by the diminishing acidity of the products as ring size is increased.

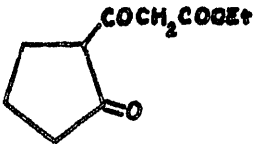
The stronger the base used, the more rapidly is the anion formed in the initial stage, and reaction is thereby promoted. The equilibrium may also be disturbed by removal of either the alcohol or the diketone from the reaction mixture, as they are formed.

Although this reaction has been used to prepare five- and six-membered cyclic 1,3-diketones, its extension to larger rings has not been recorded. Following the successful preparation of a cyclohexane-1,3-dione by this method,[72] it was hoped that cyclisation of ω-ethoxycarbonylacylacetic esters (I) might occur at the apparently more reactive carbon-2, independent of the ring size of the product, and thus provide a general route to cyclic β-diketones.

$$\underset{4}{ROOC(CH_2)_n} - \underset{4}{CH_2} - \underset{3}{CO} - \underset{2}{CH_2} - \underset{1}{COOR}$$

(I)

When Allan and Sneeden[73] cyclised 1,6-diethoxycarbonylhexan-2-one (I, n = 3, R = Et) however, condensation took place at carbon-4 and gave rise to the cyclopentanone derivative (II) instead of the desired cycloheptane-1,3-dione.



(II)

Simultaneously, Hauser and his co-workers[74] showed that with β-diketones of type (III), use of excess base caused formation of the dianion (IV), and that alkylation and acylation took place preferentially at the methyl rather than the α-methylene group. The authors[73] therefore explained the formation of the cyclopentanone derivative on the basis of the dianion (V, n = 3, R = Et) which would cyclise more readily to give the five-membered ring.

CH_3COCH_2COR (III)

$\bar{C}H_2COCHCOR$ (IV)

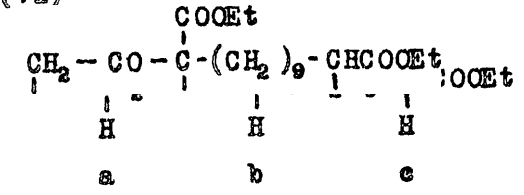
$ROOC(CH_2)_n\bar{C}HCOCHCOOR$ (V)

It is also possible that condensation at the desired centre is inhibited by enol chelate formation with an atom of sodium.

It was therefore of interest to examine the condensation of ethyl α-acetylbrassylate (VI) under similar basic conditions, since cyclisation of the dianion (VII) in this compound could give the desired cyclic β-diketone.

$CH_3CO\dot{C}H(CH_2)_{10}COOEt$ (VI)

$CH_2CO\dot{C}(CH_2)_{10}COOEt$ (VII)



(VIII)

Theoretically, ethyl α-acetylbrassylate can give rise to anions by the loss of protons from three reactive methylene groups at C_a, C_b and C_c (VIII). However, the acidity of the hydrogen atom on C_c is considerably reduced by the length of the carbon chain to which it is attached. By analogy with the results of Hauser *et al.*,[74] ethyl α-acetylbrassylate should give rise to the dianion (VII) in strong base, and condensations should take place preferentially at the terminal carbon atom. In addition, cyclisation at the methyl group would give a fourteen-membered ring, while the products of the alternative intramolecular condensations would contain the less stable twelve-membered (i.e. medium sized) ring.

An alternative cyclisation using an ω-ethoxycarbonyl-acylacetic ester of long chain length, was also envisaged to verify the dianion hypothesis and to ensure that the cyclisation of Sneeden and Allan[73] had not been directed purely by considerations of ring size.

The projected synthesis of ethyl α-acetylbrassylate (VI) involved the condensation of ethyl 11-bromoundecanoate (IX, R = Et, X = Br) with acetoacetic ester. The bromo-ester was obtained by addition of hydrogen bromide to ω-undecenoic acid (X)

under anti- Markownikoff conditions,[75] followed by azeotropic esterification. The condensation reaction with acetoacetic ester presented unexpected difficulties.

$CH_2 = CH(CH_2)_8COOH$ (X) $XCH_2CH_2(CH_2)_8COOR$ (IX)

A trial condensation of ethyl 11-bromoundecanoate and acetoacetic ester with sodium ethoxide, gave a complex mixture of starting materials and products which were not readily separable. The bromo-ester was thereupon converted to its iodo-analogue, and a trial condensation effected using the conditions employed by Ställberg-Stenhagen[76] for similar condensations between ethyl 11-iodoundecanoate and β-ketoesters, namely potassium carbonate in methyl n-propyl ketone. As only a small quantity of the condensed product was obtained, the reaction was repeated on a larger scale. On this occasion, none of the desired product was obtained, and the distilled material, which solidified on cooling, gave no copper derivative. From spectral and physical constants the product was identified as ethyl 13-ketomyristate (XI, R = Et) and this was confirmed by preparation of the semicarbazone and by hydrolysis to 13-keto-myristic acid. Robinson[77] also found that ethyl 13-keto-myristate was formed in an attempted condensation of the sodium salt of ethyl α-acetylbrassylate and hexanoyl chloride.

As ethyl 13-ketomyristate was obtained in good yield and should provide similar anions to its α-acetyl derivative, it was of interest to study the possibility of effecting a cyclisation of this ester by the action of strong base under conditions of high dilution. Once again, condensation is expected at the methyl rather than the α-methylene carbon due to the formation of the dianion (XII), especially as this would give a fourteen-membered ring, instead of the alternative twelve-membered ring.

$CH_3COCH_2(CH_2)_{10}COOR$ (XI)

$\bar{C}H_2C\bar{C}H(CH_2)_{10}COOR$ (XII)

Cyclisation of ethyl 13-ketomyristate was attempted at high dilution using a four molar excess of dry potassium t-butoxide in vigorously stirred, refluxing xylene, under anaerobic conditions.* A solution of the keto-ester in xylene was added to the base via the dilution chamber, and refluxing continued a further thirty minutes on completion of addition. The cooled reaction mixture was acidified with acetic acid, washed with water, and the organic layer evaporated to leave a yellow wax, which had a pleasant musk-like odour. By shaking an ethereal solution of the wax with aqueous copper acetate, a copper derivative was obtained in 43% yield. This material decomposed on warming and could not be recrystallised. Shaking the salt with dilute mineral acid regenerated the wax without apparent purification.

* The apparatus used is described on page 44

The wax, which gave a red-brown colouration with methanolic ferric chloride showed acidic hydroxyl, broad carbonyl and double bond absorption bands in the infrared. In the ultraviolet, the absorption maximum at 2760 Å. in neutral and acidic ethanol was displaced to 2960 Å. in alkali.

All attempts to triturate and to recrystallise this wax failed. On sublimation the amount of distillable material was negligible, the major portion being left as a dark brown gum. No simple carbonyl derivatives could be prepared. An endeavour to convert any β-dicarbonyl function present to its enol methyl ether with diazomethane, and to reduce this with lithium aluminium hydride to an αβ-unsaturated ketone, gave a hydroxylic plastic, which was insoluble in all solvents and did not give a 2,4-dinitrophenylhydrazone.

The wax was hydrolysed with base and the resulting acids esterified. Retention times on gas chromatography indicated that the mixture contained the methyl esters of 13-ketomyristic acid and brassylic acid, along with other products. Brassylic acid could arise from the hydrolysis of linear or cyclic condensation products.

The residual ether layer, after shaking the cyclisation product with copper acetate, was evaporated leaving an olive green oil. Hydrolysis of this residue by shaking with dilute

mineral acid, gave a viscous oil, whose ultraviolet and infrared spectra were very similar to those of the original cyclisation product, and which gave 13-ketomyristic acid (XI, R = H) on sublimation and recrystallisation. Alternatively, 13-keto-myristic acid could be isolated by washing the green oil from insoluble copper salts with ether, and extracting the evaporated washings with hexane. The acid was characterised by direct comparison with authentic material.

As the products of this condensation were obviously a mixture of hydrolysed starting material and polymeric compounds, the cyclisation was repeated at increased dilution. Very slow addition of ethyl 13-ketomyristate to strong base over an extended period, however, gave identical reaction products.

At this stage it was decided to revert to the originally proposed cyclisation with ethyl α-acetylbrassylate. Having failed to obtain condensation between either 11-bromo- or 11-iodoundecanoates and the morpholino enamine of acetoacetic ester, the base catalysed condensation of ethyl 11-iodoundecan-oate and acetoacetic ester was reinvestigated. With sodium ethoxide, under apparently the same conditions as used previously with the bromo-ester, the condensation was effected to give the desired homogeneous product in 80% yield.

Ethyl α-acetylbrassylate was first subjected to the high dilution reaction conditions employed for ethyl 13-ketomyristate,

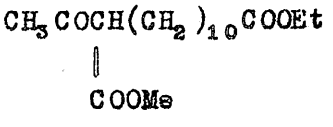
again using a four molar excess of potassium t-butoxide in xylene. As before, acidification and extraction gave a yellow wax with an odour of musk. The wax showed carboxyl, ester, carbonyl and double bond absorption in the infrared and gave a weak red-brown colour with ferric chloride. Distillation of the crude product yielded only 13-ketomyristic acid, while the greater part remained as a non-distillable tar. Conversion of the wax to a copper salt did not afford a means of purification, as this salt was not recrystallisable and the wax was regenerated unchanged. In the ultraviolet, a bathochromic shift from 2740 Å. to 2860 Å. was again obtained on addition of alkali, while with acid no shift was apparent.

The cyclisation was repeated at even greater dilution using tetrahydrofuran as solvent in order to reduce the temperature in the reaction chamber, and perhaps thereby protect any labile products formed. On this occasion the oil isolated by acidification and extraction did not give a solid derivative with copper acetate, but gave instead a blue syrup. Regeneration by shaking with mineral acid, gave a viscous oil, which was shown to be a mixture by thin layer chromatography. The oil was separated by chromatography on silica into two fractions.

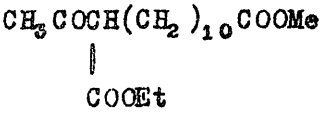
The less strongly adsorbed minor fraction was an oil which could not be distilled. It did not give a colouration with ferric chloride and from its infrared spectrum was apparently an ester.

The major fraction solidified on standing to give a waxy white solid, which, from infrared absorption, was a half acid ester. This compound could not be recrystallised, and attempted distillation gave only small amounts of distillate while leaving a large tarry residue. The distillate, again a waxy solid, showed new infrared absorption consistent with an anhydride.

As the acid gave no simple carbonyl or acid derivatives, it was converted to its methyl ester, which gave a feeble colouration with ferric chloride and did not form a copper derivative. The ultraviolet absorption of the ester was identical with that of ethyl α-acetylbrassylate. These two esters showed similar flow rates on thin layer chromatography and similar retention times when chromatographed in the vapour phase.



(XIII)



(XIV)

Analytical and nuclear magnetic resonance determinations confirmed the identity of the methylation product as one of the ethyl methyl α-acetylbrassylates (XIII and XIV).

Following the failure to obtain cyclisation of ethyl α-acetylbrassylate with potassium t-butoxide as basic condensing agent, it was decided to employ sodium hydride and a condensation was attempted at extremely high dilution in tetrahydrofuran.

The product isolated by acidification and extraction was a red oil, which gave a red colouration with ferric chloride but did not give a solid copper derivative. The oil, evidently a mixture, again showed acid absorption in the infrared. Chromatography on silica gave two major fractions, one acidic and one neutral.

The neutral fraction again left a considerable residue on attempted distillation. The extremely small distillate and the residue were both keto-esters which differed from the starting material most markedly in the introduction of a signal in the nuclear magnetic resonance spectrum at δ 3.15 (singlet). (In the distillate this was accompanied by loss of the triplet at δ 3.36). These high boiling products could not readily be characterised.

The acidic component solidified to give a low melting white wax, which could not be induced to crystallise or distil. The behaviour and properties of this wax were similar to those of the 'acid' obtained in the previous cyclisation. The corresponding methyl ester was prepared and this was shown to be identical with the ester obtained from the acid in the former cyclisation, by comparison of their spectra and retention times on gas chromatography.

The major products of the attempted cyclisation are thus identified as ethyl hydrogen α-acetylbrassylate and a polymeric ester.

The failure of similar attempts at cyclisation has been attributed[54] to the difficulty of formation of large carbocycles and to the reversible nature of base catalysed acylations. These factors suggest that, even under high dilution conditions, medium and large rings will not be formed unless the equilibrium is disturbed by immediate removal of the products. Furthermore, it would appear from results that will be discussed later (Section IIIc), that large ring β-diketones are unstable in the presence of alkoxides, undergoing conversion to α-acetylcyclanones.

Unfortunately, from the results of the present studies, it is impossible to say whether the condensation had produced linear or cyclic products. Formation of the acidic material is presumably the result of hydrolysis of condensation products.

In view of the products obtained and the experimental difficulties involved, this approach to cyclic β-diketones was abandoned.*

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* Henecka[6] attributed the failure of cyclisation of the analogous ethyl α-acetylglutarate to the relative mesomeric stabilities of the reactant and the product.

EXPERIMENTAL

Infrared spectra recorded are for liquid films, and ultraviolet spectra are for ethanolic solutions, unless otherwise stated.

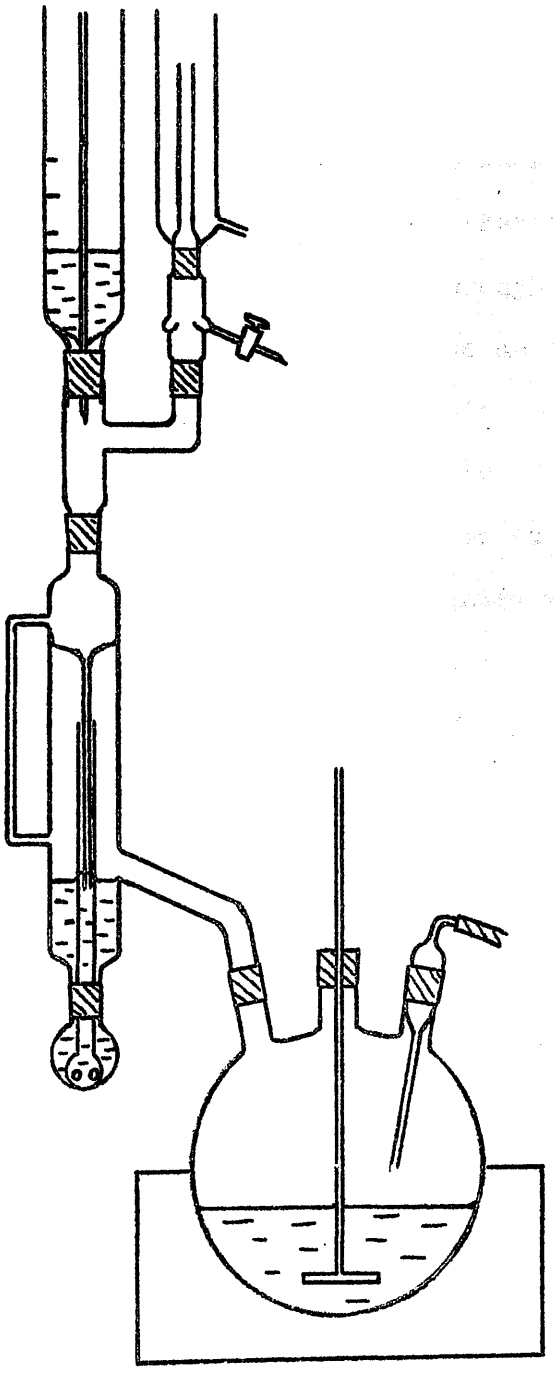
Nuclear magnetic resonance spectra are for solutions in deuterochloroform and the chemical shift δ, in p.p.m., is based on $\delta(CH_3)_4Si = 0$. The coupling constant, J, is in c.p.s.

The following contractions are used:-
s, singlet; d, doublet; t, triplet; q, quadruplet; m, multiplet; b, broad; w, weak; s, strong(I.R.).

Light petroleum refers to the fraction boiling 60-80°.

High dilution apparatus.

A diagram of the apparatus used to achieve conditions of high dilution is shown on page 44. The compound for cyclisation was added from a constant rate dropper, and flushed through the dilution chamber by refluxing solvent before entering the reaction vessel, where vigorous agitation was produced by a vibromixer.



HIGH DILUTION APPARATUS

11-Bromoundecanoic acid. (IX, R = H, X = Br)

Hydrogen bromide was prepared by addition of bromine (390 g.) to boiling tetralin (230 ml.) at such a rate as to produce a steady gaseous output, and was then freed from contamination with bromine by bubbling through tetralin. The excess of hydrogen bromide was passed into an ice-cooled solution of ω-undecenoic acid (155.0 g.) in toluene (2000 ml.), through which was passing a vigorous stream of air. On completion of the addition, the toluene was evaporated at reduced pressure to leave a blackish solid, which by repeated recrystallisation from light petroleum gave 11-bromoundecanoic acid (53.8 g.; 69%) as white plates, m.p. 49-51° (lit.,[75] m.p. 49-52°), ν_{max}^{nujol} 3400-2500, 1700, 894 (broad) and 722 cm.$^{-1}$

Ethyl 11-bromoundecanoate. (IX, R = Et, X = Br)

A solution of 11-bromoundecanoic acid (60 g.) in ethanol (82 ml.) and benzene (120 ml.) was refluxed with naphthalene-2-sulphonic acid (1.3 g.) as catalyst, and the water azeotrope run off. On cooling, the solution was washed with water, dried (Na_2SO_4), and distilled to give ethyl 11-bromoundecanoate (63.5 g.; 95%) as a colourless oil, b.p. 144-148°/0.6 mm., n_D^{23} 1.4610 (lit.,[78] b.p. 144-145°/0.5 mm.; n_D^{20} 1.4610), $\nu_{max.}$ 1735 and 722 cm.$^{-1}$

Ethyl 11-iodoundecanoate. (IX, R = Et, X = I)

Ethyl 11-bromoundecanoate (63.0 g.) in acetone (1800 ml.), was refluxed overnight with sodium iodide (134 g.). The acetone was evaporated to small bulk, and the residue taken up in ether, washed with sodium thiosulphate, water, and dried (Na_2SO_4). Distillation gave ethyl 11-iodoundecanoate (68.9 g.; 94%) as a pale yellow oil, b.p. 140-142°/0.5 mm., n_D^{16} 1.4843, $\nu_{max.}$ 1734 and 721 $cm.^{-1}$. (lit.,[79,80] b.p. 135-141°/0.5 mm.; n_D^{20} 1.4835).

Stenhagen condensation of ethyl 11-iodoundecanoate and acetoacetic ester: Ethyl 13-ketomyristate (XI, R = Et)

Methyl n-propyl ketone was dried over potassium carbonate and distilled from it before use.

A mixture of ethyl 11-iodoundecanoate (68.9 g.), acetoacetic aster (27.5 g.), and potassium carbonate (103.5 g.) in freshly dried methyl n-propyl ketone (500 ml.) was refluxed for 24 hr. The mixture was acidified (H_2SO_4) and ether extracted. The extracts were washed with sodium thiosulphate, then water, dried (Na_2SO_4), and distilled to give, as the major product, ethyl 13-ketomyristate (20.2 g.; 37%), b.p. 160-170°/1mm. (lit.[81], b.p. 164-166°/1 mm.), which solidified on cooling to a white mass, m.p. 28°, $\nu_{max.}$ 1735, 1710, and 722 $cm.^{-1}$ (Found: C,70.45; H,10.6. Calc. for $C_{16}H_{30}O_3$: C,71.05; H,11.2%).

The semicarbazone was recrystallised from alcohol as white needles, m.p. 105-106° (lit.[81], m.p. 105-106°) (Found: C, 62.15; H, 10.1; N, 12.5. Calc. for $C_{17}H_{33}N_3O_3$: C, 62.35; H, 10.15; N, 12.8%).

Ethyl 13-ketomyristate, on warming with a mixture of acetic and sulphuric acids, gave 13-ketomyristic acid as white plates (from light petroleum), m.p. 72-74° (lit.,[77] m.p. 76°), $\gamma_{max.}^{nujol}$ 3400-2400, 1710-1690 (broad twin carbonyl), 878, and 724 cm.$^{-1}$ (polymethylene chain).

Attempted cyclisation of ethyl 13-ketomyristate with potassium t-butoxide as catalyst.

The cyclisation apparatus described previously was flushed with dry nitrogen throughout the experiment. In a typical run, sodium-dried xylene (300 ml.) was placed in the reaction chamber, and a portion (ca. 50 ml.) distilled from the system, to remove any residual moisture. t-Butyl alcohol (42.9 g.), which had been refluxed over sodium and then distilled from it, was added, followed by potassium metal (10.0 g.). The mixture was refluxed till all traces of molten potassium had dissolved, and the formation of potassium t-butoxide was complete. Excess t-butyl alcohol was distilled from the system, until the refractive index of the distillate being run off at the tap was identical with that of pure xylene. Additional dry xylene was added to maintain a suitable level in the reaction chamber.

A solution of ethyl 13-ketomyristate (15.0 g.) in xylene (130 ml.) was now added from the constant rate dropper to the dilution chamber, from which it was washed by refluxing solvent into the vigorously agitated basic solution. Addition was complete after 8 hr., and was followed by an additional half-hour reflux. The reaction flask was allowed to cool and placed in an ice bath before acidification with glacial acetic acid. (A yellow solid which had formed during the addition, dissolved on acidification). After standing overnight, the xylene solution was washed repeatedly with brine, dried ($MgSO_4$), and the solvent evaporated at reduced pressure to leave a yellow wax (13.5 g.), ν_{max}^{melt} 3500-2500 (acidic hydroxyl), 1720-1690 (broad, carbonyl), 1640-1590 $cm.^{-1}$ (broad, double bond).

The wax (12.0 g.), in ether, was shaken with excess aqueous copper acetate to give a pale green copper derivative (6.7 g.; equivalent to 43% of the reaction product), which decomposed to a red oil on heating (at ~240°), $\nu_{max.}^{nujol}$ 1700 (w, carbonyl), 1565 (chelate carbonyl), and 1510 $cm.^{-1}$ (chelate double bond).

The copper derivative was shaken for 3 hr. with an ether-dilute hydrochloric acid mixture, the ethereal layer separated, dried (Na_2SO_4), and evaporated to regenerate the wax (5.0 g.), $\nu_{max.}$ unchanged, $\lambda_{max.}$ 2760 Å. (ϵ 5460), $\lambda_{max.}^{H^+}$ 2760 Å. (ϵ 5840) and $\lambda_{max.}^{OH^-}$ 2960 Å. (ϵ 10,730). [ϵ values are based on a molecular weight of 224]. The wax gave a

weak red-brown colouration with methanolic ferric chloride.

The ether layer from the copper salt preparation was evaporated to leave an olive-green oil. This product was heterogeneous, but chromatography on celite with light petroleum did not afford a separation. Attempts to redissolve the oil in ether left a small blue-coloured solid residue. The ether washings were evaporated and the residue extracted with light petroleum (40-60) to give 13-ketomyristic acid, which recrystallised from light petroleum as white plates, m.p. 71-73°, alone and admixed with an authentic specimen, $\gamma_{max.}^{nujol}$ 3400-2600 (carboxyl) and 1710-1690 $cm.^{-1}$ (keto and carboxyl carbonyls). (Found: C,68.9; H,11.2. Calc. for $C_{14}H_{26}O_3$: C,69.3; H,10.8%).

Hydrolysis of the green oil by shaking with dilute mineral acid gave a wax, whose infrared and ultraviolet spectra were very similar to those of the original condensation product. On sublimation, this wax gave small amounts of partially solid sublimate, while a large quantity of gum remained as a residue. The solid distillate was recrystallised from light petroleum and on resublimation gave 13-ketomyristic acid.

Identical products were obtained when the condensation process was carried out at higher dilution, adding 7.0 g. of ethyl 13-ketomyristate over 13 hr.

Ethyl α-acetylbrassylate (VI).

A mixture of ethyl 11-iodoundecanoate (109.6 g.) and freshly distilled acetoacetic ester (58.09 g.) was held at a temperature of 55-60°, while a solution of sodium (7.3 g.) in absolute alcohol (220 ml.) was added dropwise during one hour. The reagents were refluxed for 36 hr., by which time the solution had pH 7-8. On cooling, the products were poured into water containing a small quantity of acetic acid, and extracted with ether. The organic extract was washed with sodium thiosulphate and water, dried (Na_2SO_4), and distilled to yield ethyl α-acetylbrassylate (90.2 g.; 82%) as a colourless oil, b.p. 168-170°/0.2 mm. (lit.,[77,82] b.p. 202°/0.5 mm., 173-183°/0.09 mm), n_D^{17} 1.4498, $\nu_{max.}$ 1738, 1721, 855 (w) and 722 (w) $cm.^{-1}$ $\lambda_{max.}$ 2590 Å. (ε 480), $\lambda_{max.}^{OH^-}$ 2860 Å. (ε 13,600), (Found: C,66.45; H,10.0. Calc. for $C_{19}H_{34}O_3$: C,66.6; H,10.0%). N.M.R.: δ 4.19 (q; J = 7) δ 4.07 (q; J = 7) two $COCH_2CH_3$, δ 3.36 (t) $COCH(CH_2)CO$, δ 2.25(b) CH_3CO (enol), δ 2.16 (s) CH_3CO (keto).

Attempted cyclisations of ethyl α-acetylbrassylate.

(a) Using the same apparatus and technique as before, a solution of ethyl α-acetylbrassylate (8.41 g.) in xylene (280 ml.) was added to a solution of potassium t-butoxide [from potassium (5.7 g.) and t-butanol (70 ml.)] in xylene (500 ml.) over 17 hr. On cooling, the solution was acidified with glacial acetic acid, diluted with water, and extracted with ether.

Evaporation gave a yellow wax (6.02 g.) which smelled of musk and gave a red-brown colouration with ferric chloride. The wax was shaken in ether with aqueous copper acetate, to give an ether soluble copper salt which could not be purified. The copper salt was shaken with dilute mineral acid to regenerate the wax, $\nu_{max.}$ 3500-2800 (COOH), 1755, 1720, 1695 (ester and conj. carbonyl) and 1670-1595 cm.$^{-1}$ shoulder (double bond), $\lambda_{max.}$ 2740Å, $\lambda^{H^+}_{max.}$ 2750 Å., $\lambda^{OH^-}_{max.}$ 2860 Å. The wax decomposed to a brown tar on attempted distillation. By sublimation a small amount of 13-ketomyristic acid was obtained and recrystallised from light petroleum as white plates, m.p. 69-71°, alone or admixed with an authentic specimen.

(b) As before, ethyl α-acetylbrassylate (12.43 g.) in tetrahydrofuran (500 ml.) was added to potassium t-butoxide [from potassium (8.5 g.) and t-butanol (100 ml.)] in refluxing tetrahydrofuran (800 ml.) over 84 hr. Refluxing was continued a further 10 hr., and the solution acidified with glacial acetic acid after cooling. The mixture was poured into brine and extracted with ether. The ethereal extracts were washed with water and then shaken with an aqueous solution of copper acetate to give a waxy blue copper salt, from which the liquids were decanted. This salt, which could not be crystallised, was shaken with ether and dilute hydrochloric acid. The organic extract was dried and evaporated to regenerate a viscous oil

(6.95 g.), $\nu_{max.}$ 3400-2700, 1750, 1720, and 1650 cm.$^{-1}$. This oil gave a weak green-brown colouration with methanolic ferric chloride.

The oil (6.17 g.) was chromatographed on silica (250 g.) with benzene-chloroform (3:1), to give a neutral fraction (0.130 g.), and an acidic fraction (4.02 g.). Methanol then eluted an acidic fraction (1.28 g.), whose retention time on a chromatoplate and other properties were identical with those of the main acid fraction.

The neutral fraction was an oil, $\nu_{max.}$ 1750-1735 (esters) and 1710 cm.$^{-1}$ (weak carbonyl shoulder), $\lambda_{max.}$ 2750 Å. (ϵ 200 for M.wt. 340), $\lambda^{OH^-}_{max.}$ 2890 Å., which gave no colouration with ferric chloride and decomposed on distillation.

The acid fraction was extracted from ethereal solution with dilute sodium carbonate, and liberated by acidification and ether extraction. It was shown to be homogeneous by thin layer chromatography, and solidified on standing to a low-melting white wax, $\nu_{max.}$ 3500-2400 (COOH), 1730 (ester), 1700-1650 (weak shoulder) and 1200 cm.$^{-1}$ (b, ester), $\lambda_{max.}$ 2580 Å (ϵ 524) $\lambda^{OH^-}_{max.}$ 2850 Å. (ϵ 1476) [based on M.Wt. 314]. This material could not be recrystallised, and sublimed to a low-melting white wax $\nu_{max.}$ 3200-2650, 1815, 1730-1690 (broad), 875 and 718 cm.$^{-1}$, while leaving a considerable tarry residue.

An ethereal solution of the acid (1.45 g.) was treated

with diazomethane, dried, evaporated, and distilled to give the methyl ester (1.30 g.), b.p. 148-150°/0.4 mm, $\nu_{max.}$ 1743, 1720, 855 (w) and 722 (w) cm.$^{-1}$, $\lambda_{max.}$ 2590 Å. (ε 492), $\lambda_{max.}^{OH^-}$ 2850 Å. (ε 15,970), (Found: C, 65.9; H, 9.6. Calc. for $C_{18}H_{32}O_5$: C, 65.8; H, 9.8%), N.M.R. : δ 4.18 (q, J = 7, 2 protons) OCH_2CH_3, δ 3.62 (s, 3 protons) $-OCH_3$, δ 3.26 (t) $COCH(CH_2)CO$, δ 2.24 (b) CH_3CO (enol), δ 2.14 (s) CH_3CO (keto).

The ester did not give a colour with ferric chloride nor form a copper salt with copper acetate. With Brady's reagent, a 2,4-dinitrophenylhydrazone was obtained which remained an oil even after having been twice chromatographed from alumina.

(c) Tetrahydrofuran, which had previously been dried over sodium, was distilled from lithium aluminium hydride.

A solution of ethyl α-acetylbrassylate (11.59 g.) in dry tetrahydrofuran (300 ml.) was added to a refluxing suspension of sodium hydride (12 g. before removal of suspension oil with pet. ether) in the same solvent (1100 ml.) over 75 hr. The reaction mixture was left overnight at room temperature, and cooled in an ice bath before acidification with glacial acetic acid and dilution with water. The solution was extracted with ether, the extracts washed with sodium bicarbonate and water, dried and evaporated to leave a red oil (8.89 g.) smelling faintly of musk. This oil gave a red colouration with ferric chloride.

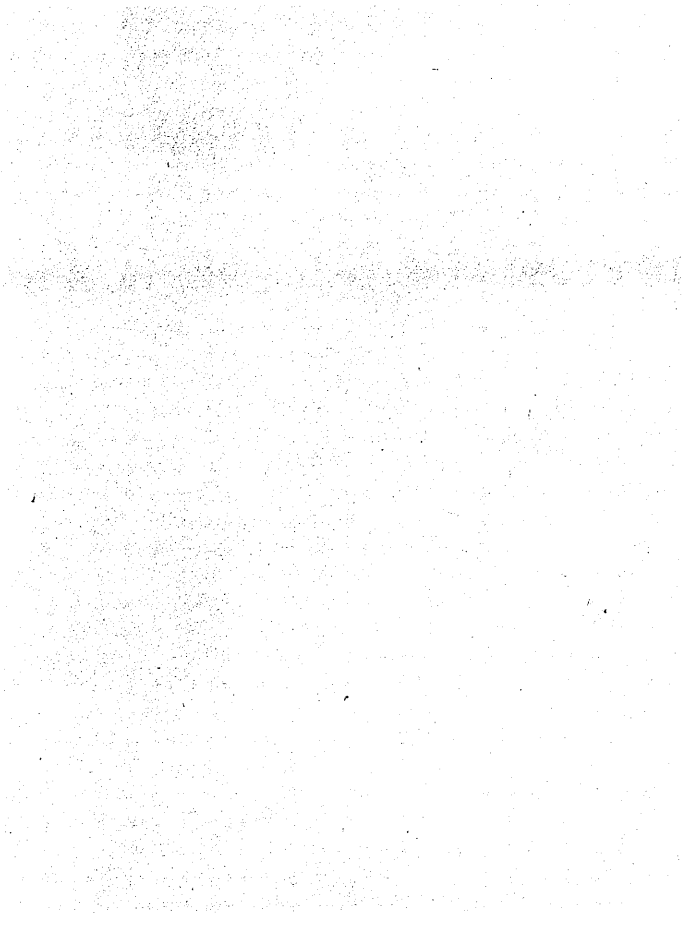
The oil (8.0 g.) was chromatographed on silica (350 g.) with a 3:1 chloroform-benzene mixture, to give as major products (1) a neutral fraction (2.02 g.), (2) an acid fraction (3.0 g.), and (3), by addition of ethyl acetate to the eluent, a further quantity of acid (2.32 g.).

The neutral fraction gave no colouration with ferric chloride nor a copper salt with copper acetate. Distillation left a considerable residue and the distillate was a colourless oil (0.210 g.), b.p. 150-160°/0.3 mm., $\nu_{max.}$ 1745-1715 (b), 1700 (shoulder) and 1200 cm.$^{-1}$ (broad ester), $\lambda_{max.}$ 2750 Å. (ϵ 255 for M = 340), $\lambda^{OH^-}_{max.}$ 2880 Å (ϵ 1650). N.M.R.: δ 4.07 at least two $-COOCH_2CH_3$., δ 3.15 (s) unassigned and δ 2.03 (s) CH_3CO- .

The distillation residue was eluted twice through an alumina (Grade III) column with benzene to leave a colourless oil, $\nu_{max.}$ 1745 and 1715 cm.$^{-1}$ (broad band), $\lambda_{max.}$ 2580 Å (ϵ459), $\lambda^{OH^-}_{max.}$ 2860 A. (ϵ 5160) (ϵ values based on a molecular weight of 340). N.M.R.: δ 4.15 (q) $COOCH_2CH_3$, δ 3.28 (t) $COCH(CH_2)CO$, δ 3.13 (s) and δ 2.12 (s) CH_3CO- .

The acidic fraction and the acidic washings from chromatography both solidified to a white wax on standing, and had properties identical to one another and to the acid obtained in the preceding cyclisation. Further confirmation of identity

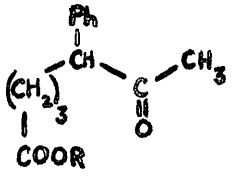
was given by comparison (analysis, thin layer and vapour phase chromatography, and nuclear magnetic resonance spectra) of the methyl esters.



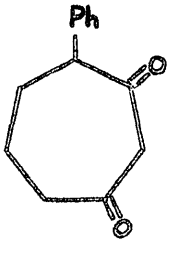
SECTION II

THE CYCLISATION OF ETHYL 6-OXO-5-PHENYLHEPTANOATE

During our investigations on the practicability of using the cyclisation of long chain keto-esters as a synthetic route to alicyclic β-diketones, the claim to have prepared an isomer of House's 2-phenylcycloheptane-1,3-dione[54] by a ring closure technique was reported. Bergmann and Yaroslavsky[83] cyclised ethyl 6-oxo-5-phenylheptanoate (I, R = Et) by means of sodium ethoxide in ethanol, and described the products, which they were able to separate with sodium carbonate, as 4-phenylcycloheptane-1,3-dione monohydrate (II, H_2O) and 2-acetyl-2-phenylcyclopentanone (III). The formation of these products might reasonably be expected by base catalysed interaction of the ester group with the two possible carbanions derivable



(I)



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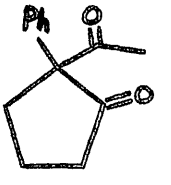


(III)

from the unsymmetrical ketone. Doubts as to the nature of these compounds, however, were raised by the properties ascribed to them, and by their incomplete documentation.

The solubility of the reported 4-phenylcycloheptane-1,3-dione (II) in sodium carbonate was in full accord with the Eistert

concept of 'trans-fixed' β-diketones[8], which behave as vinylogous acids. This assignment was supported by an intense broad hydroxyl absorption in the infrared. The simultaneous report that this compound gave a strong violet colouration with ethanolic ferric chloride was, however, in complete contradiction to this structural assignment. Complex formation with metal ions is a measure of the cis-enolisability of a β-dicarbonyl compound and is precluded by 'trans-fixing', which obtains in a ring of this size. Further, a violet colouration with ferric chloride is generally accepted as indicative of α-alkylsubstitution of a β-diketone[6], since such a substitution causes a shift in the extinction maximum towards the red. By comparison, House's 2-phenylcycloheptane-1,3-dione was little enolised, and gave no colouration with ferric chloride.

Inconsistencies in the analytical data for the reported 4-phenylcycloheptane-1,3-dione were unsatisfactorily explained by its formulation as a monohydrate. In addition, the enol ether obtained by attempted ketalisation with ethylene glycol and that from azeotropic distillation with ethanol, both had analyses explicable only on the unsatisfactory basis of a firmly bound molecule of water.

While the analytical data for the reported 2-acetyl-2-phenylcyclopentanone (III) were satisfactory, the carbonyl absorption in the infrared at 1717 $cm.^{-1}$ seems low for a cyclopentanone. Also, under strongly basic conditions the

direction of a reversible reaction is generally determined by the relative acidities of the species involved, the equilibrium being disturbed to give that anion which has the lowest basicity. It is therefore surprising that under basic conditions one should obtain 2-acetyl-2-phenylcyclopentanone, which, by virtue of its αα-disubstitution can neither enolise nor give rise to a mesomerically stabilised anion, and is hence non-acidic.

In order to clarify these anomalies it was decided to repeat the cyclisation of ethyl 6-oxo-5-phenylheptanoate and re-examine the products.

Ethyl 6-oxo-5-phenylheptanoate (I, R = Et) was prepared by a synthetic route identical to that employed by Bergmann and Yaroslavsky.[83] Butyrolactone was treated with hydrogen bromide and the product esterified without prior separation. The ethyl γ-bromobutyrate so obtained was converted to its iodo-analogue and this was condensed with phenylacetone by means of sodium hydride in a mixture of benzene and dimethylformamide, to give ethyl 6-oxo-5-phenylheptanoate. The purity of the latter was established by the quantitative preparation of its 2,4-dinitrophenylhydrazone, and its structure confirmed by hydrolysis to an acid $C_{13}H_{16}O_3$, which gave a positive iodoform test. (This excludes the alternative formulation, 6-oxo-7-phenylheptanoic acid, for the hydrolysis product.) Absolute confirmation was

given by the nuclear magnetic resonance spectrum (see Experimental) which showed the presence of a methyl ketone grouping.

Ethyl 6-oxo-5-phenylheptanoate (I, R = Et) was cyclised according to the conditions of Bergmann[83], to give yields of a carbonate soluble and a carbonate insoluble product similar to those previously described. In agreement with the earlier findings, no simple carbonyl derivatives were obtained.

The Carbonate Soluble Fraction

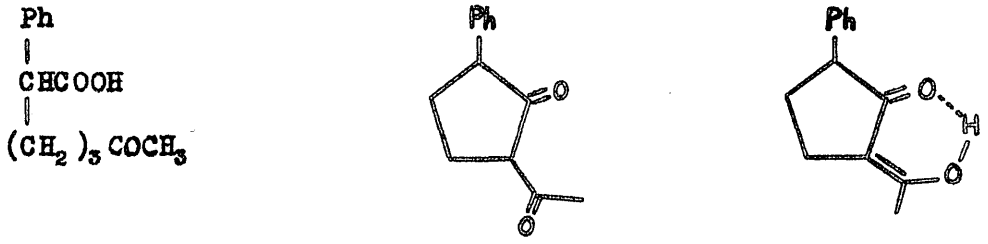
This material gave a weak violet colouration with methanolic ferric chloride and had the properties and spectra previously ascribed to 4-phenylcycloheptane-1,3-dione monohydrate (II, H_2O). While the analysis obtained was in complete accord with that of Bergmann, it did not correspond to the data required either by the diketone, or by its monohydrate. It was observed during distillation of this material, that the arbitrary fractions collected were not homogeneous. Indeed, the higher boiling fractions did not give a violet colouration with ferric chloride, and an infrared absorption maximum observed in the lower fractions at 1650 $cm.^{-1}$ was absent. A sample of the carbonate soluble fraction gave a green oil when shaken with an aqueous solution of copper acetate. Chromatography of this oil on celite and hydrolysis by shaking with dilute mineral acid gave an acid which

did not form a coloured complex with ferric chloride. The presence of a carboxylic acid in the crude carbonate soluble product was indicated by infrared dilution studies.

It was found on the basis of these results, that the carbonate soluble fraction was a mixture, which could be separated into two components either by careful fractionation or, more readily, by sodium bicarbonate extraction. The acid component was identified as 6-oxo-5-phenylheptanoic acid (I, R = H) by direct comparison, the authentic specimen being obtained by hydrolysis of the starting material. This component, which gave no colour reaction with ferric chloride, comprised 85-90% of the carbonate soluble fraction.

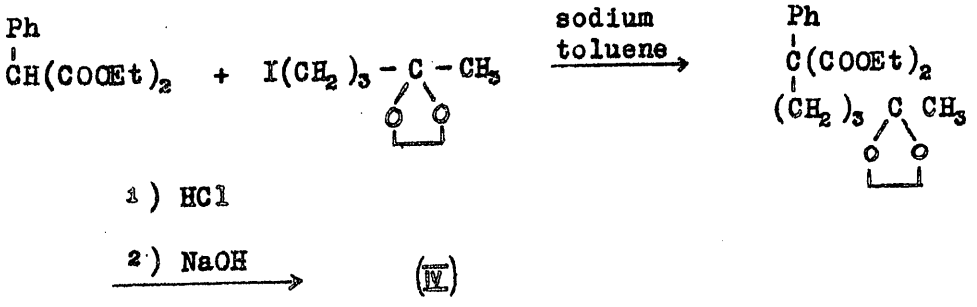
The remaining 10-15% of acidic, but bicarbonate insoluble material $C_{13}H_{14}O_2$, gave an intense violet colouration with methanolic ferric chloride. The molecular weight of this compound was confirmed by mass spectroscopy. Its nuclear magnetic resonance spectrum indicated the presence of a phenyl group (δ 7.1-7.24, m, 5 protons) and a methyl ketone (keto form, δ 2.2, s ; enol form, δ 1.9). This together with the ultraviolet spectrum in neutral ($\lambda_{max.}$ 2450 and 2880 Å.) and in alkaline solution ($\lambda_{max.}$ 2420 and 3110Å.) identified the compound as a phenyl-2-acetylcyclopentanone. Alkaline hydrolysis of this

component gave 6-oxo-2-phenylheptanoic acid (IV), which was identified by direct comparison with an authentic specimen. This bicarbonate insoluble component must therefore be a mixture of the keto and enol forms of 2-acetyl-5-phenylcyclopentanone (V and VI). As the trans position is occupied by a ring carbon, this compound is a 'cis-fixed' β-diketone, and can therefore readily chelate and form metal complexes. In addition, it has an α-substituent which explains the violet colouration obtained with methanolic ferric chloride.



(IV) (V) (VI)

The authentic specimen of 6-oxo-2-phenylheptanoic acid (IV) was prepared by base catalysed condensation of diethyl phenylmalonate with the ketal of 5-iodopentan-2-one, followed by first acidic and then basic hydrolysis.



The Carbonate Insoluble Fraction.

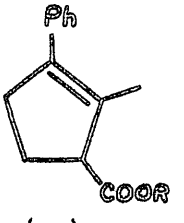
In our hands, the carbonate insoluble fraction from the cyclisation of ethyl 6-oxo-5-phenylheptanoate possessed the molecular formula $C_{15}H_{18}O_2$, and the molecular weight (230) was confirmed by mass spectroscopy. (2-Acetyl-2-phenylcyclopentanone (III) has molecular formula $C_{13}H_{14}O_2$ and molecular weight 202). With methanolic ferric chloride it gave a very pale green colouration. The infrared spectrum of this compound indicated the presence of a phenyl group, a conjugated double bond and an ester group. The presence of a double bond was further confirmed by ultraviolet absorption at 2420Å. (ϵ 10,780)+ and by the formation of a scarlet colour with tetranitromethane. Catalytic hydrogenation of the double bond gave the dihydro-compound $C_{15}H_{20}O_2$, which was almost transparent in the ultraviolet and gave no colouration with tetranitromethane.

The unsaturated ester, $C_{15}H_{18}O_2$, was hydrolysed with base to give the corresponding acid, $C_{13}H_{14}O_2$, which was characterised as its crystalline amide and anilide. Attempts to decarboxylate the acid with copper bronze failed. The nuclear magnetic resonance spectrum of the anilide° indicated the presence of a phenyl group (δ 7.39 and 7.34), an allylic

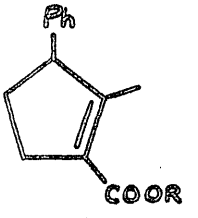
+ The spectral data given by the previous authors was limited to an indication of a broad carbonyl absorption in the infrared at 1717 $cm.^{-1}$.

° The chemical shift δ, in p.p.m., is based on $\delta(CH_3)_4Si = 0$ in CF_3COOH.

proton (δ 3.98, m), allylic methylene (δ 2.91, m), allcyclic methylene (δ 2.35, m) and an allylic methyl group (CH_3-C=C) (δ 1.92, m). The infrared spectrum of the anilide indicated the presence of an unconjugated amido grouping ($\nu_{max.}^{CCl_4}$ 1695 cm.$^{-1}$), and the ultraviolet spectrum ($\lambda_{max.}$ 2500 Å.) established that the double bond was in conjugation with the aromatic nucleus. This compound must therefore be the anilide (VII, R = NHPh) of 2-methyl-1-phenylcyclopent-1-ene-3-carboxylic acid (VII, R = H).



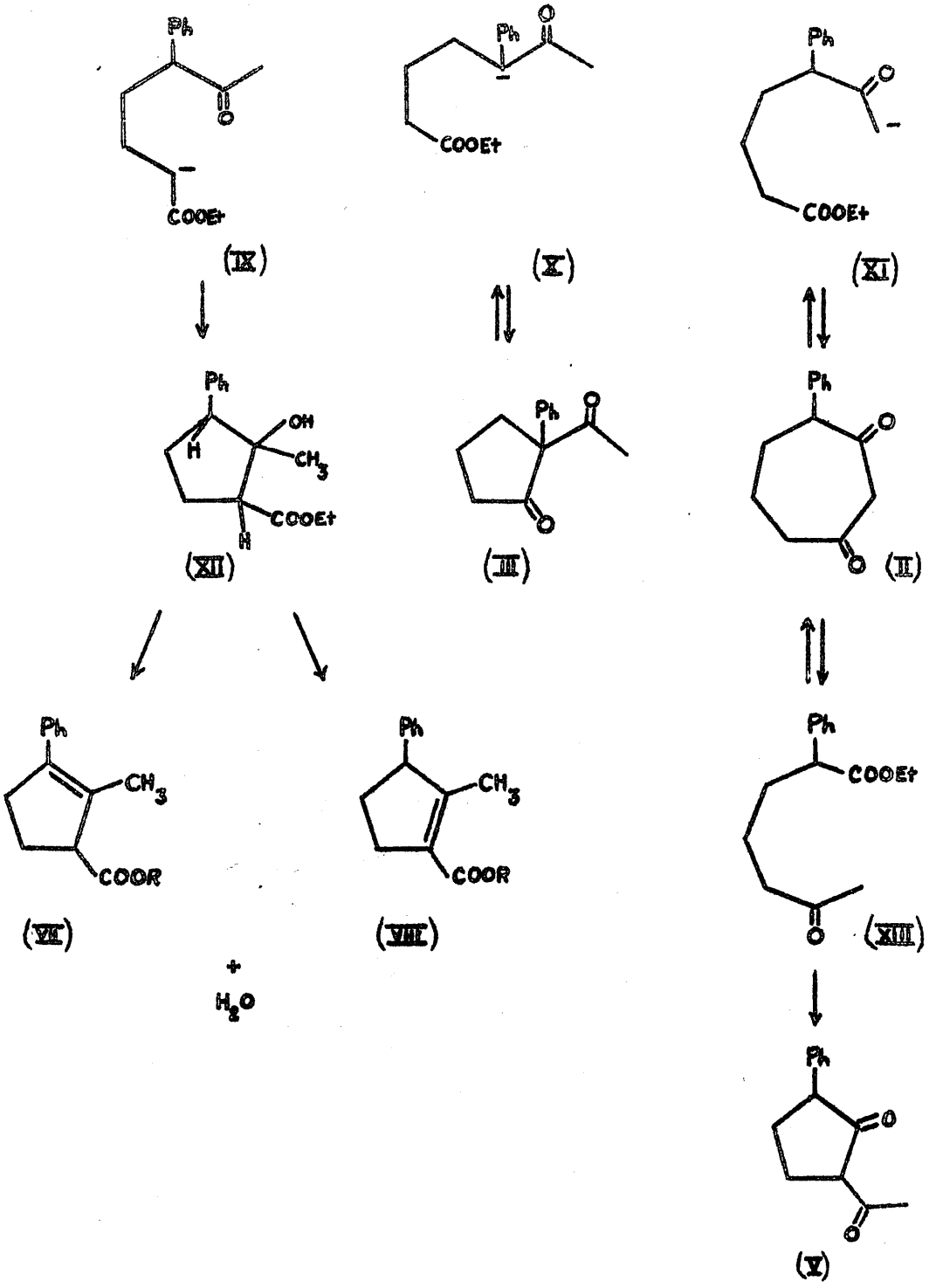
(VII)



(VIII)

The parent ethyl ester, however, exhibits infrared absorption in chloroform at 1730 cm.$^{-1}$ (alkyl ester), a shoulder at 1710 cm.$^{-1}$ (conjugated ester), and 1645 cm.$^{-1}$ (conjugated double bond). Its nuclear magnetic resonance spectrum also shows the presence of two distinct ethoxycarbonyl groups (δ 1.26 and 1.28, two triplets each with J = 7; δ 4.11 and 4.15, two quadruplets each with J = 7). These facts establish that the ester is a mixture of the isomers VII (R = Et) and VIII (R = Et).

Attempts to oxidise the ester by the Lemieux technique


Ph
COOEt
(IX)
(X)
(XI)
OH
CH3
H
(XII)
(III)
(II)
COOR
(VII)
(VIII)
(XIII)
+
H2O
(V)

or with permanganate in acetone having failed, it was ozonised and the product obtained converted to its 2,4-dinitrophenylhydrazone. The constants of the ozonolysis product would indicate that it is ethyl γ-benzoylbutyrate.

The formation of these reaction products by treatment of ethyl 6-oxo-5-phenylheptanoate with base may be rationalised in the following manner.

In the presence of sodium ethoxide the ester (I) (R = Et) can give rise to three anions (IX), (X), and (XI).

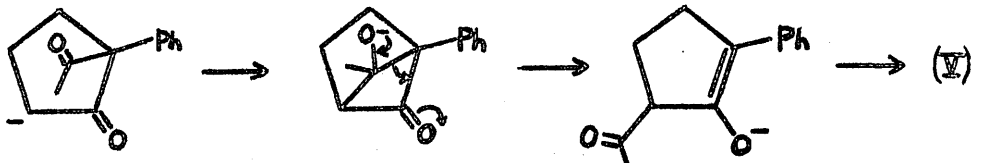
Anion (IX) can cyclise to the alcohol (XII), in which two protons are available for irreversible dehydration to the isomers (VII) (R = Et) and (VIII) (R = Et). The water produced in this reaction would be removed from the system by the hydrolysis of the ester (I) (R = Et) to the corresponding acid.

Anion (X) could cyclise to the non-enolisable 1,3-diketone (III). The latter, however, would be readily cleaved with sodium ethoxide in ethanol, regenerating the ester (I) (R = Et).

Anion (XI) can cyclise to the cycloheptane-1,3-dione (II), which, however, might not be stable to sodium ethoxide and

ethanol[*], and could undergo cleavage either to the original ester (I)(R = Et) or to the ester (XIII). The latter can cyclise to the stable, enolisable 1,3-diketone (V).

The above scheme accounts satisfactorily for the formation of all the observed products. However, the work of Pinder and Robinson[84] on non-enolisable 1,3-diketones suggests an alternative route which could account for the formation of (V). The anion (XIV), of the non-enolisable 1,3-diketone (III) could undergo rearrangement to give (V) in the following manner:-



(XIV)

[*] It will be seen from later results (Section IIIc) that cycloheptane-1,3-dione is not stable towards ethoxide.

EXPERIMENTAL

Ethyl γ-bromobutyrate.

Butyrolactone (100 g.) in ethanol (60 ml.) and benzene (120 ml.) was saturated with gaseous hydrogen bromide, prepared by dropwise addition of bromine (436 g.) to boiling tetralin (400 ml.). The solution was then azeotropically distilled until no more water was evolved, and, when cool, poured into 0.1N sodium hydroxide and crushed ice. After a further wash with base, the organic layer was washed with water and dried ($MgSO_4$). Distillation gave ethyl γ-bromobutyrate (162 g.; 71%) as a pale yellow oil, b.p. 88-89°/ 10 mm. (lit.[83], b.p. 98-100°/20 mm.).

Ethyl γ-iodobutyrate.

Ethyl γ-bromobutyrate (162 g.) was shaken in acetone (700 ml.) with sodium iodide (164 g.) for 3 hr. After filtration of excess sodium iodide, the acetone was evaporated to small bulk and the residue taken up in benzene. The benzene solution was washed with sodium bisulphite and water, and dried. Evaporation of the solvent and distillation gave ethyl γ-iodobutyrate (174.4 g.; 87%) as a yellow oil, b.p. 107-110°/23 mm. (lit.[83] b.p. 100-101°/ 20 mm.).

Ethyl 6-oxo-5-phenylheptanoate (I, R = Et).

With the temperature held at 5°, phenylacetone (88 g.) was added dropwise over 20 min., to a vigorously stirred

mixture of sodium hydride (15.5 g.), dry benzene (250 ml.) and anhydrous dimethylformamide (250 ml.). Effervescence indicated that the reaction was in progress. On completion of the addition, stirring was continued for a further 20 min., before ethyl γ-iodobutyrate (174.4 g.) was added dropwise while the temperature was held at 10°. The reaction mixture was slowly warmed to 50° and maintained at between 50-60° for 6 hr. After cooling, ethanol (25 ml.) and then water was added, and the organic layer washed with sodium bisulphite and water. The dried ($MgSO_4$) extract was distilled through a short column to give ethyl 6-oxo-5-phenylheptanoate (62 g., 40%) as a clear oil, b.p. 118°/0.03 mm., n_D^{24} 1.4970, (Found: C, 72.55; H, 7.8. Calc. for $C_{15}H_{20}O_3$: C, 72.6; H, 8.0%), $\lambda_{max.}$ 2200, 2620 and 2850Å. (ε 5660, 256 and 285), $\nu_{max.}$ 1725 (alkyl COOEt), 1710 (alkyl C = O), 1600, 1495, 760 and 704 $cm.^{-1}$ (phenyl), N.M.R.: δ 1.19 (t, J = 7), δ 4.03 (q, J = 7) CH_3CH_2 of COOEt, δ 1.96 (s) CH_3 of CH_3CO, δ 3.57 (t, J = 7) H of PhCH-, δ 7.22 (m) C_6H_5.

2,4-Dinitrophenylhydrazone of I (R = Et).

Ethyl 6-oxo-5-phenylheptanoate (2.47 g.) in methanol was treated with excess Brady's reagent, the whole diluted with water and extracted with chloroform. Chromatography of the dried extract on alumina (Grade III) with benzene, gave

980 $cm.^{-1}$ (Found: C, 74.1 ; H, 10.3. $C_{13}H_{22}O_2$ requires C, 74.25; H, 10.55%).

Further elution with benzene-chloroform (1:3) gave the hydroxy-ketones (39 a + b, R= H), (14.5 g.) as a mixture of epimers, m.p. 35-50°, $\nu_{max.}$ (in Nujol) 3500-3350, 1700, 1060-1040, and 980 $cm.^{-1}$ (see also Part II), (Found: C, 72.25; H, 9.75. $C_{11}H_{18}O_2$ requires C, 72.50; H, 9.95%).

A solution of the mixed hydroxy-ketones (3.97 g.) and toluene-p-sulphonyl chloride (4.20 g.) in pyridine (10 ml.) was warmed on a steam-bath for 1 hr., and kept at room temperature for 15 hr., then diluted with ethyl acetate (50 ml.) and water (50 ml.). The separated organic layer was washed with dilute hydrochloric acid, saturated sodium carbonate solution, and dried. Removal of solvent gave a pale yellow solid, 6.5 g., m.p. 110-130°, which was fractionally crystallised from benzene-light petroleum. The early crops (1.5 g.) crystallised from ethanol as colourless plates to give one epimeric toluene-p-sulphonate m.p. 145-146° (decomp.), $\nu_{max.}$ (in Nujol) 1710, 1350, 1190, 1180, 923, 900 amd 875 $cm.^{-1}$ (Found: C, 64.0; H, 7.4. $C_{18}H_{24}O_4S$ requires C, 64.25; H, 7.2%). Later fractions (3.0 g.) crystallised from ethanol to give the second pure epimeric toluene-p-sulphonate as colourless plates, m.p. 114-115°, $\nu_{max.}$ (in Nujol) 1710, 1350, 1190, 1180, 943, 870 and 817 $cm.^{-1}$ (Found: C, 64.15; H, 7.2%).

the 2,4-dinitrophenylhydrazone (3.61 g.; 86%) as golden yellow needles, m.p. 96.5-97.5° (MeOH) [Lit.,[83] m.p. 78°]. (Found: C,58.7; H,5.8; N,13.1. $C_{21}H_{24}N_4O_6$ requires C,58.9; H,5.65; N,13.1%).

6-Oxo-5-phenylheptanoic acid. (I, R = H).

The ester (I) (R = Et; 1.97 g.) was readily hydrolysed by refluxing with 10% sodium hydroxide (20 ml.) to give the acid as a viscous clear oil (1.44 g.; 82%), b.p. 143-147°/0.4 mm., (Found: C,71.1; H,7.4. $C_{13}H_{16}O_3$ requires C,70.9; H,7.3%), $\lambda_{max.}$ 2510, 2600, and 2840 Å. (ϵ 302, 309 and 315), $\nu_{max.}$ 3200-2650, 1715-1700, 1600, 1495, 760 and 700 $cm.^{-1}$. The acid gave a positive iodoform test, thereby excluding its possible formulation as 6-oxo-7-phenylheptanoic acid.

The acid formed a semicarbazone, m.p. 182-183° (from aqueous ethanol). (Found: C,60.8; H,7.05; N,15.25. $C_{14}H_{19}N_3O_3$ requires C,60.6; H,6.9; N,15.15%).

Regenerated from the semicarbazone, the acid was obtained as a colourless solid, m.p. 35-37.5° .

Cyclisation of ethyl 6-oxo-5-phenylheptanoate.

Following the technique of Bergmann,[83] ethyl 6-oxo-5-phenylheptanoate (I, R = Et; 19.47 g.) was added dropwise to a refluxing solution of sodium ethoxide (from sodium [1.73 g.] in 40 ml. dry ethanol). The mixture was

refluxed a further two hours before cooling and acidification with glacial acetic acid. After dilution with water, the ethereal layer was extracted with sodium carbonate (5N) to give a carbonate soluble fraction (6.54 g.; 41.2%) and a carbonate insoluble fraction (8.60 g.; 54.2%). [These yields are for crude material and are based on products of molecular weight 202].

Carbonate soluble fraction.

Carbonate extraction of the cyclisation products gave a colourless, viscous, oil, b.p. 160-166°/0.45 mm., (Found: C,71.8; H,7.45. Calc. for $C_{13}H_{14}O_2$: C,77.2, H,7.0. Calc. for $C_{13}H_{14}O_2.H_2O$.: C,71.0; H,7.3. Lit. values[83]: C,72.1; H,7.3%), $\nu_{max.}$ 3200-2650, 1740-1700, 1600, 1495, 760, and 704 cm.$^{-1}$ This material gave a weak violet colour with methanolic ferric chloride.

Further separation of this oil was possible either by careful fractional distillation, or, more readily, by extraction with sodium bicarbonate.

Bicarbonate Soluble.

Acidification, extraction, and distillation of the bicarbonate extracts gave 6-oxo-5-phenylheptanoic acid, b.p. 130-140°/ 0.09 mm. (Found: C,70.6; H,7.5. $C_{13}H_{16}O_3$ requires C,70.9; H,7.3%) U.V. and I.R. spectra were identical with those reported above for 6-oxo-5-phenylheptanoic acid. A positive iodoform test was again obtained.

The semicarbazone, alone and admixed with an authentic specimen, had m.p. 182-185° (Found: C, 60.6; H, 6.9; N, 15.05. $C_{14}H_{19}N_3O_3$ requires C, 60.6; H, 6.9; N, 15.15%). Hydrolysis of this derivative regenerated the acid, m.p. 35-39°.

Bicarbonate insoluble.

The ethereal layer after bicarbonate extraction gave, on drying and distillation, 2-acetyl-5-phenylcyclopentanone (as a mixture of keto and enol forms) b.p. 114-116°/0.04 mm. (Found: C, 77.0; H, 7.2. $C_{13}H_{14}O_2$ requires C, 77.2; H, 7.0%), $\lambda_{max.}$ 2450, 2880 Å. (ϵ 3438 and 5693) $\lambda_{max.}^{OH^-}$ 2410, 3110 Å. (ϵ 3602 and 14,860), $\nu_{max.}$ 1740 (5-membered cyclic C =O), 1705 (acyclic C = O), 1650 (conj. C = O), 1605 (conj. C = C), 1595, 1500 760, and 700 cm.$^{-1}$ (Ph).

The material gave an intense violet colouration with methanolic ferric chloride.

Hydrolysis of bicarbonate insoluble fraction.

Hydrolysis of the bicarbonate insoluble fraction with 10% sodium hydroxide gave 6-oxo-2-phenylheptanoic acid, b.p. 142-148°/0.07 mm. (Found: C, 71.45; H, 7.55. $C_{13}H_{16}O_3$ requires C, 70.9; H, 7.3%), $\nu_{max.}$ 3300-2600, 1720, 1700, 1600, 1495, 760, and 700 cm.$^{-1}$. The acid gave a positive iodoform test.

The semicarbazone crystallised from ethanol as prisms, m.p. 164-165°, alone or admixed with an authentic specimen.

(Found: C, 60.4; H, 6.7; N, 14.9. $C_{14}H_{19}N_3O_3$ requires C, 60.6; H, 6.9; N, 15.15%).

6-Oxo-2-phenylheptanoic acid (IV).

5-Chloropentan-2-one[85] (93 g., b.p. 62-64°/12 mm., n_D^{17} 1.4394) and ethylene glycol (124 ml.) in benzene (450 ml.) containing p-toluenesulphonic acid (1 g.) were refluxed in a Dean-Stark apparatus. When no more water separated (12 hr.) the cooled solution was washed with 1N sodium hydroxide (2 x 50 ml.), water (3 x 50 ml.), dried (Na_2SO_4) and fractionally distilled to yield the ethylene ketal of 5-chloropentan-2-one (109 g.) as a colourless oil, b.p. 92°/12 mm., n_D^{20} 1.4501.

The chloroketal (109 g.), sodium iodide (400 g.), and acetone (2.3 litres) were stored overnight at room temperature. The acetone was removed by slow distillation, the residue diluted with water, and ether extracted. The extracts were washed with sodium bisulphite(to remove free iodine), water, and then dried (Na_2SO_4) and distilled. The ketal of 5-iodopentan-2-one (40 g.) was obtained as a colourless oil, b.p. 108-110°/12 mm., n_D^{26} 1.4840. The oil darkened rapidly on standing and was therefore used immediately.

Diethyl phenylmalonate (29.75 g.) was added dropwise to a refluxing suspension of sodium (2.95 g.) in toluene (200 ml.) with vigorous stirring. Refluxing was continued a further 30 min. before cooling. The ketal of 5-iodopentan-2-one (33.1 g.) was

added over 40 min. and the solution stirred and refluxed a further 6 hr. The cooled solution was washed with water, dried (Na_2SO_4), and distilled to give the ketal of ethyl 2-ethoxycarbonyl-6-oxo--2-phenylheptanoate (14.9 g.), b.p. 150-154°/0.15 mm., n_D^{22} 1.4970. (Found: C,66.25; H,7.8. $C_{20}H_{28}O_6$ requires C,65.9; H,7.75%), $\nu_{max.}$ 1740, 1360, 1070, 1040,945 and 690 $cm.^{-1}$.

The ketal-ester (2.21 g.) was left overnight in aqueous methanolic hydrochloric acid (20 ml.), diluted with water and ether extracted. On evaporation of the ether, the extract was refluxed with 10% sodium hydroxide (20 ml.) for two hours, and the cooled solution washed with ether, acidified, and extracted with ether to give 6-oxo-2-phenylheptanoic acid (1.16 g.; 87%) b.p. 150-154° 0.2 mm., $\nu_{max.}$ 3000-2600, 1720 and 1700 $cm.^{-1}$

The semicarbazone, from ethanol, had m.p. 164-165° (Found: C,60.5; H,6.7; N,15.1. $C_{14}H_{19}N_3O_3$ requires C,60.6; H,6.9; N,15.15%).

Carbonate insoluble.

The organic layer from the cyclisation of(I, R = Et) after washing with carbonate, was dried and evaporated to give an inseparable mixture of 3-ethoxycarbonyl-2-methyl-1- phenyl--2-ene, b.p. 102-104°/ 0.05 mm., n_D^{24} 1.5439 (Found: C.78.25; H,7.9. $C_{15}H_{18}O_2$ requires C,78.25; H,7.9%), $\lambda_{max.}$ 2420 Å. (ε 12,300),

H,7.9. $C_{15}H_{18}O_2$ requires C,78.25; H,7.9%), $\lambda_{max.}$ 2420 Å. (ε 12,300),

$\nu_{max.}^{CCl_4}$ soln. 1734, 1710 and 1645 cm.$^{-1}$. The oil gave a reddish brown colour with tetranitromethane.

The above mixture of esters was hydrolysed with 10% sodium hydroxide (50 ml.) to give 2-methyl-1-phenylcyclopent--1-ene-3-carboxylic acid and 2-methyl-1-phenylcyclopent-2-ene-3-carboxylic acid, b.p. 134-136°/0.1 mm., n_D^{24} 1.5660 (Found: C,76.8; H,7.1. $C_{13}H_{14}O_2$ requires C,77.2; H,7.0%), $\lambda_{max.}$ 2370 Å. (ϵ 5580). $\nu_{max.}$ 3300-2650, 1700 (broad), 1655, 1600, 1500, 760, and 705 cm.$^{-1}$ The p-nitrobenzyl ester was an oil.

Anilide and amide of 2-methyl-1-phenylcyclopent-1-ene-3-carboxylic acid.

The non-conjugated acid was characterised as its crystalline anilide and amide as follows. The acid chloride was formed in benzene with oxalyl chloride and a drop of pyridine. The anilide was obtained by treatment of the acid chloride in ether with freshly distilled aniline, and was recrystallised from aqueous ethanol as white plates, m.p. 172-173°, (Found: C,82.0; H,6.9; N,5.05. $C_{19}H_{19}NO$ requires C,82.3; H,7.1; N,5.1%), $\nu_{max.}^{CCl_4}$ soln. 3440, 3398 (NH of secondary amine) and 1695 cm.$^{-1}$ (CO of unconjugated amido grouping), $\lambda_{max.}$ 2500 Å. (ϵ 30,470). N.M.R. is detailed in the discussion.

The amide, also obtained via the acid chloride, recrystallised from aqueous ethanol as pale yellow plates, m.p. 147-148° (Found: C,77.8; H,7.6; N,6.7. $C_{13}H_{15}NO$ requires

C, 77.6; H, 7.5; N, 7.0%), $\nu_{max.}^{CCl_4}$ soln. 3540, 3414 (NH_2 of primary amine), and 1698 cm.$^{-1}$ (CO of unconjugated amido group), $\lambda_{max.}$ 2490 Å. (ϵ 12,880).

Hydrogenation of the mixed esters.

The ester mixture was hydrogenated with palladium charcoal (10%) in ethanol to give a mixture of the stereoisomers of 1-ethoxycarbonyl-2-methyl-3-phenylcyclopentane as a colourless oil, b.p. 92-93°/ 0.05 mm. (Found: C, 77.55; H, 9.0. $C_{15}H_{20}O_2$ requires C, 77.55; H, 8.7%), $\lambda_{max.}$ 2590 Å. (ϵ 256), $\nu_{max.}$ 1720, 1600, 1495 and 705 cm.$^{-1}$ The hydrogenation product gave no colouration with tetranitromethane or ferric chloride.

Ozonolysis of the mixed esters.

The mixed 3-ethoxycarbonyl-2-methyl-1-phenylcyclopentenes (1.92 g.) in chloroform (30 ml.) were ozonised at -60° for 20 mins. On warming to room temperature, the blue colour of the solution disappeared. The chloroform was removed under reduced pressure at room temperature, and the ozonide decomposed by addition of glacial acetic acid (30 ml.), followed by zinc in small portions. The residue was diluted with water and extracted with ether. The extracts were washed with sodium bicarbonate, water, and dried (Na_2SO_4). Evaporation gave ethyl γ-benzoylbutyrate (1.93 g.), b.p. 128-132°/0.07 mm. (lit.,[86] b.p. 178-180°/ 10 mm.), $\lambda_{max.}$ 2430 Å. (ϵ 6400) (cf. lit.,[87] for γ-benzoylbutyric

acid $\lambda_{max.}$ 2420 Å.), $\nu_{max.}$ 3400 (weak OH), 1730, 1720, 1685 (phenyl ketone), 1600, 915, 765 and 700 cm.$^{-1}$.

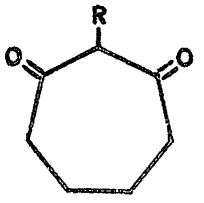
The ester on treatment with Brady's reagent, gave a mixture of 2,4-dinitrophenylhydrazones, which was diluted with water and extracted with chloroform. The dried (Na_2SO_4) organic extract was evaporated, and the residue chromatographed on alumina (Grade III) with benzene and benzene-chloroform mixture. The major fraction was recrystallised from ethanol to give the 2,4-dinitrophenylhydrazone of ethyl γ-benzoylbutyrate as red needles, m.p. 122-123° (lit,[86] m.p. 126-127°), $\lambda_{max.}$ 3750 Å (ε 24,720) (Found: C,56.95; H,5.1; N,13.75. Calc. for $C_{19}H_{20}O_6N_4$: C,57.0; H,5.05; N,14.0%).

In a typical experiment, cyclisation of ethyl 6-oxo-5-phenylheptanoate (29.66 g.) with sodium ethoxide gave 6-oxo-5-phenylheptanoic acid (7.98 g., 31%), 2-acetyl-5-phenylcyclopentanone (1.00 g., 4%) and a mixture of 3-ethoxycarbonyl-2-methyl-1-phenylcyclopent-1-ene and 3-ethoxycarbonyl-2-methyl-1-phenylcyclopent-2-ene (10.40 g., 38%). [Yields are based on purified reaction products].

SECTION III

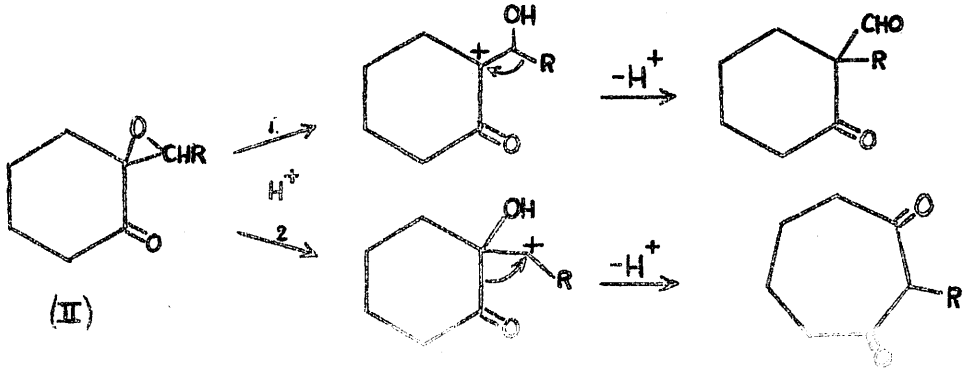
CYCLOHEPTANE-1,3-DIONE

(a) Following the controversy arising from the nature of the cyclisation products of ethyl 6-oxo-5-phenylheptanoate and in order to study more fully the properties of a β-dicarbonyl function in a seven-membered ring, the preparation of the then unknown cycloheptane-1,3-dione (I, R = H) was undertaken.



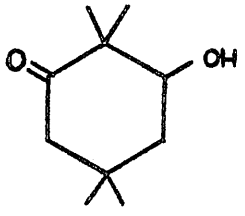
I

The only previously reported cycloheptane-1,3-dione was the 2-phenyl derivative (I, R = Ph) prepared by House and Wasson.[54] Earlier work on the isomerisation of αβ-epoxyketones with boron trifluoride etherate to give β-dicarbonyl compounds,[88] was expanded by these authors to include cyclic ketones. In the acyclic series, the use of isotopic tracers had shown that acyl migration was involved, and that the migration was intramolecular.[89] Theoretically, the acid catalysed rearrangements of cyclic αβ-epoxyketones of type (II) can occur in two ways:-

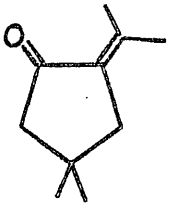


(II)

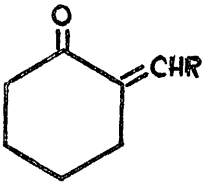
The carbonium ion produced in path (1) however, contains two adjacent carbon atoms each of which is bearing at least partial positive charge in violation of Pauling's adjacent charge rule,[90] thus making its formation and the subsequent alkyl migration unlikely. Acyl migration by path (2) is therefore to be expected. Moreover, in an analogous case, Eschenmoser and his co-workers found that dehydration of 3-hydroxy-2,2,5,5-tetramethylcyclohexanone (III) with concentrated sulphuric acid gave 2-isopropylidene-4,4-dimethyl-cyclopentanone (IV),[91] i.e. the product of acyl rather than alkyl migration.



(III)



(IV)



(V)

House and Wasson[54] prepared the corresponding epoxides from 2-benzylidenecyclanones by reaction with alkaline hydrogen peroxide. Treatment of the epoxides with boron trifluoride etherate gave the 2-phenylcyclane-1,3-diones expected, by preferential migration of the acyl group.

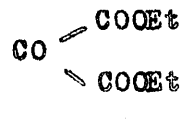
2-Phenylcycloheptane-1,3-dione (I, R = Ph) prepared by

this method from 2-benzylidenecyclohexanone (V, R = Ph), exhibited properties inconsistent with 'trans-fixed' theory. It gave no colouration with methanolic ferric chloride and in ethanol showed only weak ultraviolet absorption at 2660 Å. (ϵ 3,100, which suggests around 30% enolisation). In the infrared, twin carbonyl absorption maxima were apparent at 1695 and 1721 cm.$^{-1}$ (shoulder) and no hydroxyl peak was observed.

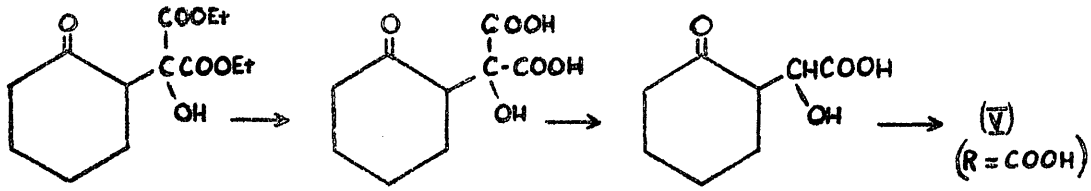
It was not possible to say whether this lack of enolisation and of 'trans-fixed' character was a consequence of ring size, or whether it was due to the phenyl substituent inhibiting enolisation on steric grounds.

An analogous route to that employed by House was envisaged for the preparation of cycloheptane-1,3-dione itself (I, R = H). It was hoped that isomerisation of the epoxide (II, R = COOH) of 2-oxocyclohexylideneacetic acid (V, R = COOH) would give cycloheptane-1,3-dione-2-carboxylic acid (I, R = COOH), which should undergo ready decarboxylation to the desired cycloheptane-1,3-dione (I, R = H).

The preparation of 2-oxocyclohexylideneacetic acid (V, R = COOH) was first reported by Rosenmund, Glet and Pohl,[92] by condensation of cyclohexanone and diethyl mesoxalate (VI). The resulting diethyl (2-oxocyclohexyl)tartronate (VII) was hydrolysed by base, and the product decarboxylated and dehydrated to give the desired acid (V, R = COOH).

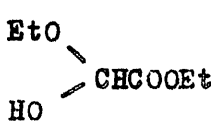


(VI)

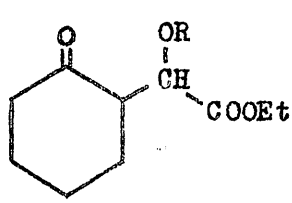


(VII)

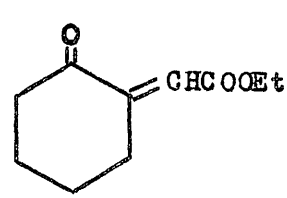
An alternative synthesis was developed by Shemyakin and his co-workers[93], who condensed cyclohexanone and the ethyl hemiacetal of ethyl glyoxylate (VIII) in pyridine, to obtain the mixed stereoisomers of ethyl 2-oxocyclohexylglycolate (IX, R = H). Formation of the acetyl derivatives (IX, R = CH_3CO) and deacetoxylation with triethylamine gave a mixture of the ethyl esters of cis- and trans- 2-oxocyclohexylidene acetic acids (X). Separation of the stereoisomers was readily effected at this stage by treatment with dimethylamine, when the trans- ester underwent quantitative conversion to ethyl threo-2-oxocyclohexyl-N,N-dimethylglycine (XI), while the cis-ester was completely unreactive. Hydrolysis of the esters (X) with mixed acetic and hydrochloric acids liberated the free 2-oxocyclohexylidene acetic acids.



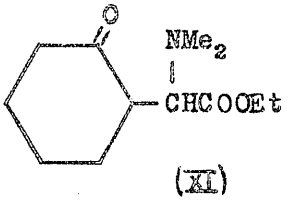
(VIII)



(IX)



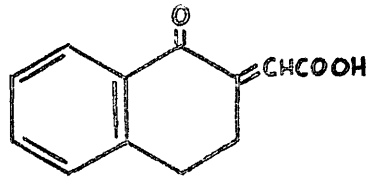
(X)



(XI)

Noltes and Kögl[94] also examined the condensation of alicyclic ketones with the ethyl hemiacetal of ethyl glyoxylate. These authors found that the moderate yields obtained using pyridine or acetic anhydride as catalysts could be greatly improved by simply heating the reagents alone at 200° in a closed system, using a large excess of the keto-compound. Although they prepared ethyl 2-oxocyclohexylglycolate (IX, R = H) in 71% yield by this method, and dehydrated it with potassium bisulphate to give ethyl 2-oxocyclohexylideneacetate (X) they did not attempt hydrolysis of the latter. A considerable high boiling residue remained on distillation of the condensation products, and was attributed to secondary condensation at the other α-methylene group.

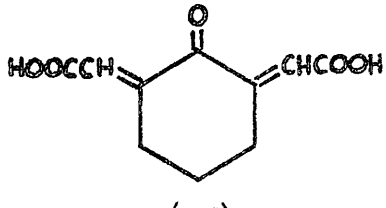
The direct condensations of glyoxylic acid and its esters with ketones have been achieved in improved yield by Newman and his co-workers,[95] by preparation of the acid <u>in situ</u>. Thus, by addition of α-tetralone to an aqueous alkaline solution of glyoxylic acid prepared <u>in situ</u> by periodate oxidation of tartaric acid,[96] 1-oxo-1,2,3,4-tetrahydro-2-naphthylideneacetic acid (XII) was obtained in 60% yield.



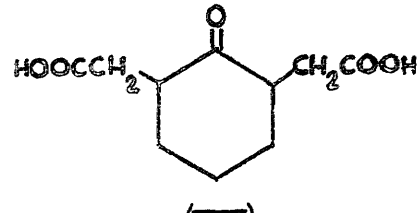
(XII)

As this last synthetic route involved only one step and avoided the tedious preparation of ethyl glyoxylate hemiacetal, it was decided to adapt it to the preparation of 2-oxocyclohexylideneacetic acid.

The preparation of 2-oxocyclohexylideneacetic acid (V, R = COOH) was attempted by direct condensation of cyclohexanone with glyoxylic acid (which had been prepared <u>in situ</u> from tartaric acid and sodium periodate in an acidic medium) following the successful technique of Newman.[95] The reaction product extracted after an extended period of stirring was not the expected acid. Instead, a powdery yellow solid was obtained which from its infrared spectrum was an unsaturated keto-acid, and this was finally identified as 1,3-di(carboxymethylene)-cyclohexan-2-one (XIII), which would result from attack by a molecule of glyoxylic acid at both of the α-methylene groups.



(XIII)



(XIV)

The diacid decomposed with decarboxylation when warmed even under reduced pressure, and was generally insoluble in all hydrocarbon solvents but exceedingly soluble in polar solvents. Recrystallisation was finally accomplished from petroleum ether-ethyl acetate, analytical data being satisfactory both before and after recrystallisation. Characterisation of 1,3-di(carboxymethylene)cyclohexan-2-one proved difficult as it did not give simple carbonyl derivatives, and attempts to prepare ester derivatives produced oils. The diacid did not react directly with simple amines, and warming with oxalyl chloride in an attempt to obtain the acid chloride caused decomposition. An amine salt was obtained however with cyclohexylamine, from which the diacid could be regenerated by shaking with mineral acid.

The uptake of hydrogen on catalytic hydrogenation of the crude acid was somewhat less than that calculated, and unsaturated impurities were evident in the product (from ultraviolet and infrared spectra and colour with tetranitromethane). By washing with ether and subsequent recrystallisation of the residue, an analytical sample of the known[97] 1,3-di(carboxymethyl)cyclohexan-2-one (XIV) was finally obtained.

1,3-Di(carboxymethylene)cyclohexan-2-one (XIII) contains

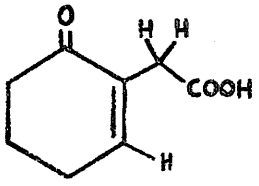
the functional group originally sought, and one might expect it to undergo epoxidation and rearrangement analogous to that outlined above for the monoacid, and thereby give a 1,3-diketone or perhaps, by a two stage process, a 1,3,5-triketone.

Accordingly, the diacid (XIII) was treated with a large excess of hydrogen peroxide under alkaline conditions.[54] Continuous ether extraction of the acidified reaction mixture gave a pungent smelling oil which solidified on standing at 0°. This material could not be crystallised and decomposed with gaseous evolution on attempted vacuum distillation, leaving a tarry residue. No simple carbonyl or acid derivatives were obtained, and the acid salt formed with 2-amino-2-methylpropanol decomposed on contact with the atmosphere. Esterification of the acidic product gave a mixture of keto-esters, which were chromatographed on alumina and sublimed. The absence of ultraviolet absorption (other than carbonyl) in the acidic product or the esters derived from it indicated that no αβ-epoxyketone had been formed.

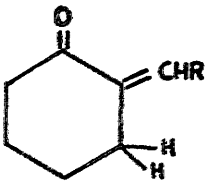
A trial sample of the epoxidation product when treated with boron trifluoride again gave acidic products, separable only by continuous ether extraction. This acidic portion, and the esters derived from it, exhibited only monoketone absorption in the ultraviolet.

On account of the failure to obtain 2-oxocyclohexylidene-acetic acid (V, R = COOH) by direct condensation of cyclohexanone with glyoxylic acid, it was decided to prepare this compound via its ethyl ester. Ethyl glyoxylate, obtained by the action of lead tetra-acetate on diethyl tartrate, was converted to its ethyl hemiacetal (VIII). (The hemiacetal is preferred to the ester as starting material as it is less susceptible to autoxidation). Ethyl glyoxylate hemiacetal and excess cyclohexanone were heated at 200° in a sealed tube,[94] but the expected 2-oxocyclo-hexylglycolate (IX, R = H) was not obtained. The product showed no hydroxyl absorption in the infrared and the spectrum was unchanged after refluxing with potassium bisulphate, indicating that spontaneous dehydration had taken place to give ethyl 2-oxocyclohexylideneacetate (X). Hydrolysis with a mixture of concentrated hydrochloric and glacial acetic acids gave 2-oxo-cyclohexylideneacetic acid (V, R = COOH), which was so soluble in dilute mineral acid that the solution could be washed free from unhydrolysed impurity with ether. Evaporation of the acidic residue left a brown solid from which the desired acid was extracted with boiling light petroleum. The properties of the acid so obtained corresponded to those reported by Shemyakin and his coworkers[93] for the cis-isomer of 2-oxocyclo-hexylideneacetic acid (V, R = COOH).

The characterisation of this compound is not, however, unambiguous, and the data quoted could reasonably satisfy the alternative structure 6-oxocyclohex-1-enylacetic acid (XV).



(XV)



(V)

Indeed, interpretation of the nuclear magnetic resonance spectrum of the acid (see Experimental) would appear to favour this isomer. The signal at δ 6.9 attributed to an ethylenic proton is a multiplet and not the well defined triplet which one would expect with 2-oxocyclohexylideneacetic acid (V, R = COOH) from splitting by the allylic ring methylene. With the isomer (XV) the signal will be split by both the ring and side chain methylene groups. In addition, the peak at δ 3.23 is apparently a doublet and is far removed from the main body of the methylene signal. It is most reasonably interpreted as due to the CH_2COOH protons of structure (XV), which lie between an unprotonated carbon atom and a carboxyl group but which will be split by the vinylic ring proton. The spectrum more closely resembles that of cyclohex-1-enylacetic acid (XVI) than that of cyclohexylidene-acetic acid (XVII).*

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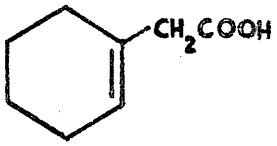
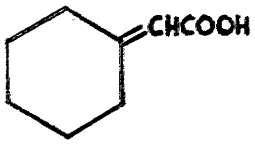
* Dr. R. P. A. Sneeden, E. T. H., Zurich, personal communication.



(XVI)



(XVII)

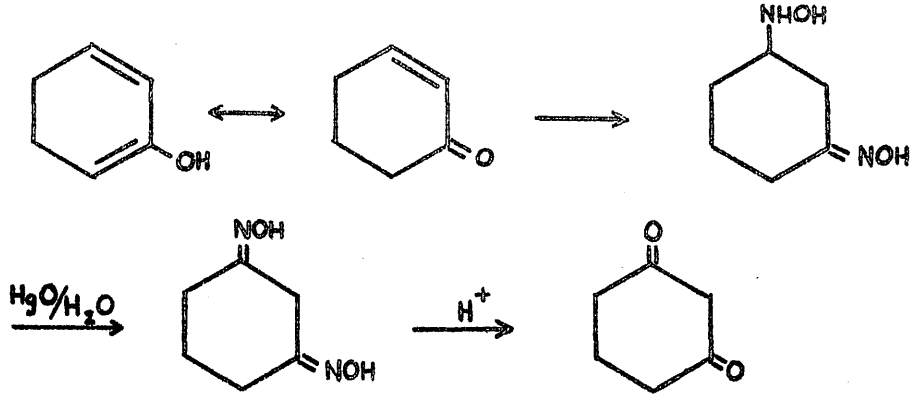
As before, the acid was treated with excess alkaline hydrogen peroxide and the acidic product extracted. Analytical data of the amine salt of this acid with 2-amino-2-methylpropanol and spectral properties of the acid regenerated from it, indicated that the desired epoxy-product had not been obtained.

As the preliminary experiments on the formation and rearrangement of these epoxy-compounds under the conditions employed by House and Wasson[54] led to intractable products, this route to cycloheptane-1,3-dione was abandoned in favour of a more fruitful route suggested by the work of Chapman and Fitton.[108]

(b) In the evaluation of the properties of cycloheptane-1,3-dione (Section IIIc), reference is made to the instability of an αβ-unsaturated ketone in a seven-membered ring, resulting from the steric resistance to coplanarity. The ready interconversion of the αβ- and βγ-isomers of cycloheptenone (XVIII) as observed by Braude and Evans[100] is a further demonstration of this phenomenon.

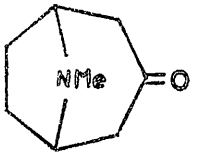
a (XVIII) b

The preparation of cyclohept-2-enone (XVIIIa) and of cyclohept-3-enone (XVIIIb) was undertaken to examine the equilibration of these isomers in acidic and basic media, and further, to investigate the possibility of using the 2-enone as a precursor to cycloheptane-1,3-dione. A precedent for this approach has been reported by Kötz and Grethe,[26] who prepared cyclohexane-1,3-dione from cyclohex-2-enone, by treatment with hydroxylamine, oxidation of the resulting 3-hydroxylamino-oxime to the dioxime, and subsequent hydrolysis.



This series of reactions suggests an alternative general synthesis of cyclic β-diketones, whose pre-requisite is a reasonably accessible supply of the αβ-cyclenones.

Cycloheptenone was first obtained as a degradation product of tropinone (XIX),[101-103] though it was some time before the so-called 'tropilene' was identified by reduction to cycloheptanone.[101] Kötz *et al*[104] prepared cycloheptenone from



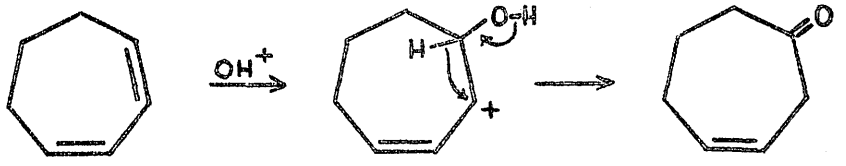
(XIX)

cycloheptanone, by bromination followed by dehydrobromination with aniline. This technique has been modified by Braude and Evans,[100] who used chlorine instead of bromine to reduce dihalogenation, and by Treibs and Grossmann,[105] who chlorinated the ketal of cycloheptanone.

The formation of cycloheptenone by the route of Braude and Evans,[100] was confirmed by hydrogenation. An analytically pure sample, however, showed ultraviolet absorption

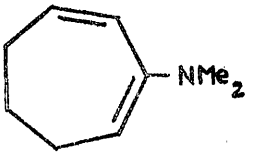
at 2270 Å., whose intensity (ε 5000-8000) was only about half that anticipated for cyclohept-2-enone (XVIIIa). Its semicarbazone showed ultraviolet absorption compatible with that expected for a mixture of the derivatives of a conjugated and of an unconjugated enone. The cycloheptenone thus prepared contained both the αβ- and βγ - isomers (XVIII a and b).

Derivatives of the isomers of cycloheptenone have been obtained by careful purification, but the isolation of a pure parent isomer has only been reported since our investigation. Recently, Cope and his co-workers[106] have described the preparation of pure cyclohept-3-enone by oxidation of cycloheptadiene with peracetic acid, and suggest the following mechanism:-



The product absorbed in the infrared at 1707 and 1650 cm.$^{-1}$ and in the ultraviolet at 2840 Å. (ε80). It gave a semicarbazone, whose melting point agreed with that reported for cyclohept-3-enone by Braude and Evans,[100] and a 2,4-dinitrophenylhydrazone, $\lambda_{max.}^{CHCl_3}$ 3600 Å. (ε 22,000), typical of such an unconjugated derivative. Identity was further verified by reduction with lithium aluminium hydride to an alcohol whose retention time on vapour phase chromatography differed from that of cyclohept-2-enol,

A sample of the mixed αβ- and βγ -isomers of cycloheptenone was made available by hydrolysis of the enamine 2-dimethylaminocyclohepta-1,3-diene (XX) ('β-methyltropidine'), derived from the degradation of tropinone (XIX).[103] Arbitrary fractions of the distilled product showed increasing refractive



(XX)

indices within the limits recorded by Braude and Evans.[100] Hydrogenation gave cycloheptanone, identified as its 2,4-dinitrophenylhydrazone by direct comparison with an authentic specimen.

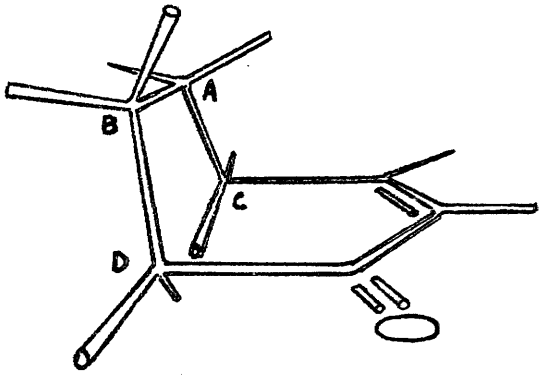
Separation of the isomers from contaminants and from one another was achieved by vapour phase chromatography to give cyclohept-2-enone [$\lambda_{max.}$ 2280 Å. (ϵ 10,060); $\nu_{max.}$ 1670-1655 and 1635 cm.$^{-1}$] and cyclohept-3-enone [$\lambda_{max.}$ only weak carbonyl absorption; $\nu_{max.}$ 1704 and 1660 cm.$^{-1}$]. The skeletal structure of both compounds was established by catalytic reduction to cycloheptanone, identified as before.

Recovery from the preparative column was small, even when acetone-drikold traps were used, and the overall yield of the pure cycloheptenones extremely disappointing. Attempts to use the mixed cycloheptenones in the Kötz and Grethe synthesis[26] led to intractable tars.

Cycloheptenone prepared by the method of Treibs and Grossmann[105] was also examined. Cycloheptanone was chlorinated and the monochloro-compound converted to its ethylene ketal. Dehydrochlorination with potassium hydroxide and hydrolysis of the ketal with oxalic acid gave the mixed cycloheptenones. Treatment with Brady's reagent followed by chromatography, gave as the major product, the 2,4-dinitrophenylhydrazone of cyclohept-2-enone. An attempt to separate the enone mixture by spinning band distillation gave an enrichment of the cyclohept--2-enone content [$\lambda_{max.}$ 2280 Å. (ϵ 7070)], but purification was incomplete. From this mixture pure cyclohept-2-enone was again obtained in poor yield by repeated vapour phase chromatography.

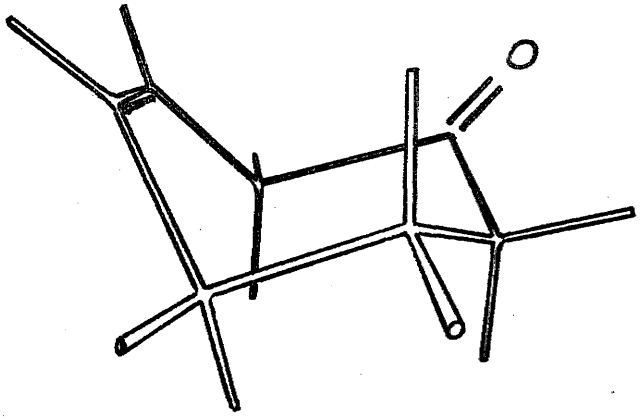
Both cycloheptenones were relatively stable to dilute acid. The ultraviolet absorption of an ethanolic solution of cyclohept-2-enone to which a drop of dilute acid had been added, changed only slowly, falling to half its original intensity after 5 days. However, addition of a drop of alkali to an ethanolic solution of this isomer, caused rapid equilibration at room temperature. After only two hours the extinction coefficient had fallen to 2,500 and rapidly reached an equilibrium value of ca. 1,000. This ready isomerisation of the $\alpha\beta$-unsaturated ketone (XVIIIa) is a reflection of the steric strain occasioned by the coplanarity of the enone system in a

seven-membered ring. Molecular models demonstrate that coplanarity requires eclipsed conformations at carbon atoms A and B, and 1,4-transannular interaction between the hydrogen atoms on carbon atoms C and D.



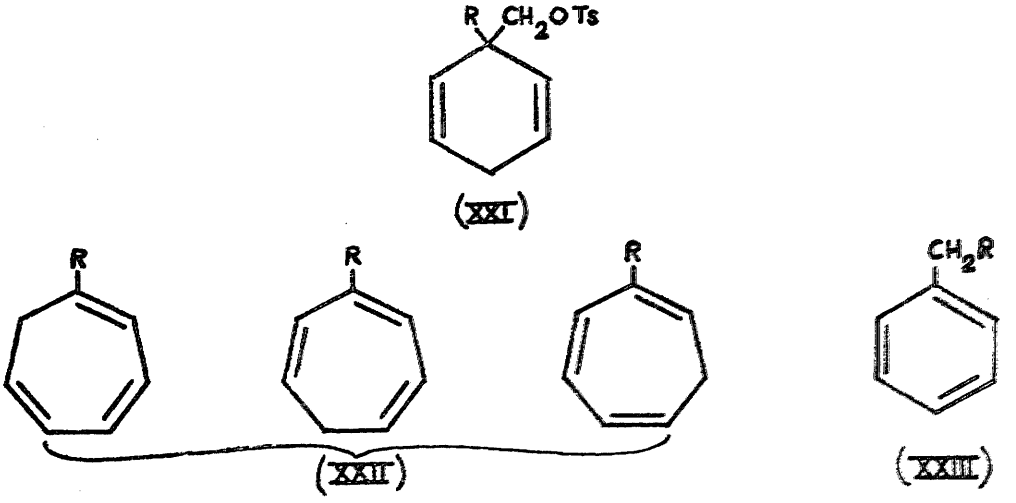
(XVIII a)

In the $\beta\gamma$ -isomer (XVIIIb) the double bond is accommodated in the ring without a great increase in strain.



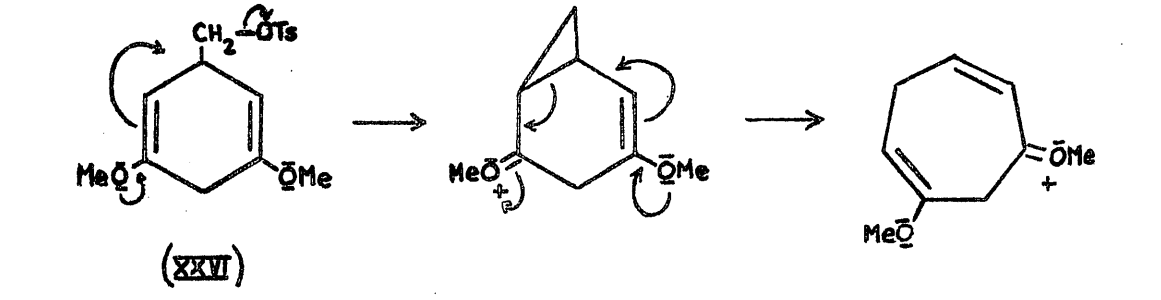
(XVIII b)

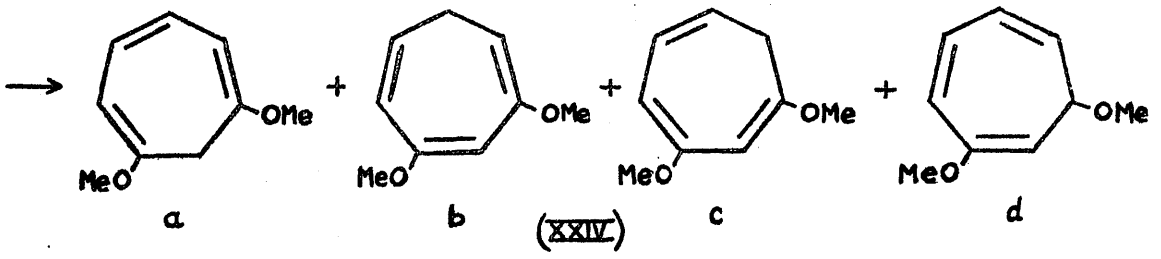
(c) The finally successful synthesis of cycloheptane-1,3-dione (unfortunately applicable only to this cyclic β-diketone) involved a solvolytic ring expansion technique, initially developed by Nelson, Fassnacht and Piper.[107] These authors converted 1,4-dihydrobenzyl alcohols to their p-toluenesulphonyl derivatives (XXI), which were then solvolysed to give as major products the isomeric cycloheptatrienes (XXII), contaminated with small amounts of toluene derivatives (XXIII).

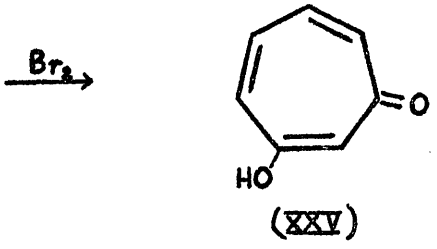


By varying the substitution of the 1,4-dihydrobenzyl alcohol, a considerable range of seven-membered ring compounds was made accessible. Chapman and Fitton[108] have recently adapted this ring expansion technique to provide a general synthetic route to troponoid compounds, by using the appropriate methoxylated compounds. Thus, from 1,4-dihydro-3,5-dimethoxybenzyl alcohol, these authors prepared an isomeric mixture of

1,3-dimethoxycycloheptatrienes (XXIV), which by oxidation with bromine provided the first practical synthesis of β-tropolone (XXV). Donation of electrons by methoxyl groups at the 3- and 5- positions of the tosylate of a 1,4-dihydrobenzyl alcohol (XXVI) will favour the required ionic displacements and increase the rate of solvolysis. Isomerisation may occur either during the solvolysis or on distillation of the crude product.

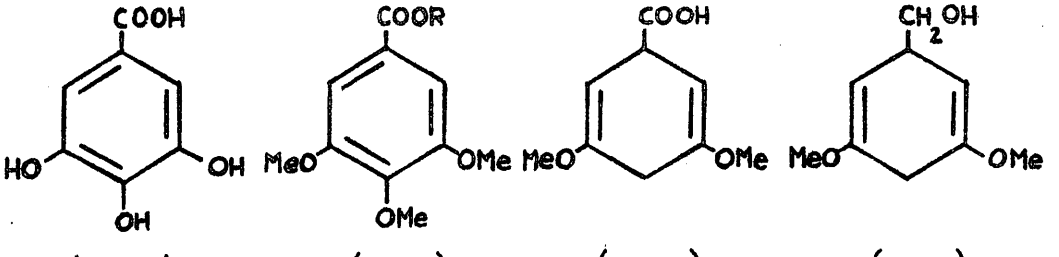






The formation of isomeric 1,3-dimethoxycycloheptatrienes was of especial interest. By virtue of the 1,3-disubstitution pattern and the electronic properties of the substituents, the three most favoured isomers (XXIV a, b, and c) contain two trisubstituted double bonds and one disubstituted double bond. Providing no isomerisation ensues, preferential reduction of the least-substituted double bond should afford a dienol ether of cycloheptane-1,3-dione, hydrolysis of which would then provide a route to the β-diketone.

The isomeric mixture of 1,3-dimethoxycycloheptatrienes was accordingly prepared by a route similar to that employed by Chapman and Fitton.[108] Gallic acid was methylated to give the methyl ester of 3,4,5-trimethoxybenzoic acid (XXVIII, R = Me), and the free acid (XXVIII, R = H) liberated by refluxing overnight with base. The acid was reduced with simultaneous



(XXVII) (XXVIII) (XXIX) (XXX)

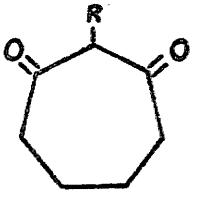
elimination of the 4-methoxyl group, using sodium and liquid ammonia under the conditions described by Kuehne and Lambert,[109] to give 1,4-dihydro-3,5-dimethoxybenzoic acid (XXIX). The yields obtained for this stage were extremely variable, and at no time approached those reported. The acid (XXIX) was then reduced with lithium aluminium hydride under anaerobic conditions to furnish 1,4-dihydro-3,5-dimethoxybenzyl alcohol (XXX). The alcohol was converted to its tosyl derivative (XXVI), which decomposed if allowed to become dry and was consequently solvolysed immediately in refluxing pyridine to give disappointing yields of 1,3-dimethoxycycloheptatrienes (XXIV). The presence of impurities was demonstrated by vapour phase chromatography (which exhibited one major and three minor peaks on a 1% silicone column), by weak carbonyl absorption in the infrared at 1710 and 1650 $cm.^{-1}$, and by secondary ultraviolet absorption at 2420 Å. As this material decomposed on standing, it was decided to proceed without further purification.

Catalytic hydrogenation with 10% palladium charcoal gave a mixture of 1,3-dimethoxycycloheptadienes(XXXI), which again

(XXXI)

exhibited two major and three minor peaks on vapour phase chromatography. Conjugated carbonyl absorption was apparent in the infrared at 1640 cm.$^{-1}$, and an ultraviolet absorption maximum at 2530 Å. was shifted, with enhancement of intensity, to 2880 Å. by addition of a drop of base. A sample of the hydrogenation product, on standing overnight in the acid conditions of Brady's reagent, gave a derivative which analysed correctly for the bis- 2,4-dinitrophenylhydrazone of cycloheptane-1,3-dione, but whose melting point was considerably lower than that of the specimen subsequently prepared.

Attempted hydrolysis of a methanolic solution of the diethers (XXXI) with dilute mineral acid, gave a keto-acid whose infrared spectrum showed no double bond characteristics, while hydrolysis attempts by shaking the diether with amberlite resin, which had previously been washed with acid and base, proved ineffective. However, gentle warming in aqueous oxalic acid for several hours brought about hydrolysis to give pure cycloheptane-1,3-dione (I, R = H).

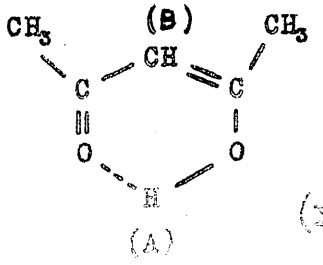


(I)

In contrast to the highly crystalline cyclohexane-1,3-dione, cycloheptane-1,3-dione was found to be a high boiling

oil, whose purification was complicated by its extremely hygroscopic nature.[53] Only when combustions were carried out on freshly distilled specimens were satisfactory analyses obtained, and the β-diketone was more conveniently characterised as its crystalline bis-2,4-dinitrophenylhydrazone and bis-oxime.

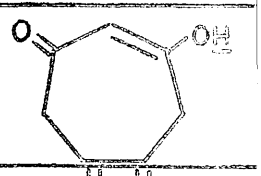
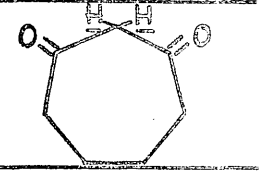
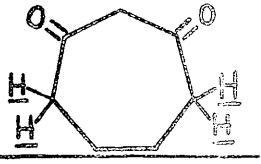
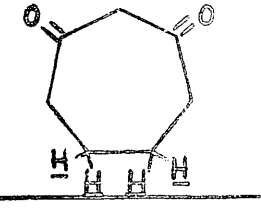
Nuclear magnetic resonance spectra of cycloheptane-1,3-dione were recorded in several solvents (see Table III). In carbon tetrachloride the spectrum showed a singlet at δ 3.51 corresponding to two protons ($-COCH_2CO-$), and two multiplets, each corresponding to four protons, at δ 2.54 and δ 2.05 ($.CH_2CH_2CO-$ and $CH_2CH_2CH_2$ respectively). In addition a weak signal at δ 4.23 appeared to indicate around 6% of the enol. Not only did this peak disappear on deuteration but that at δ 3.51 was also rapidly exchanged, and the residual signal after sixteen hours deuteration was a small distorted triplet. This triplet presumably resulted from the superimposition of a singlet due to $COCH_2CO$ and the 1:1:1 triplet of $-COCHDCO-$, with an H-D coupling constant of about 2 c.p.s. This exchange is in contrast to the behaviour of acetylacetone (XXXII), in which proton A is rapidly exchanged but proton B is only slowly affected. In '<u>trans</u>-fixed' β-diketones replacement of hydrogen



(A)

TABLE III

Main peaks in the nuclear magnetic resonance spectra of cycloheptane-1,3-dione in various solvents.

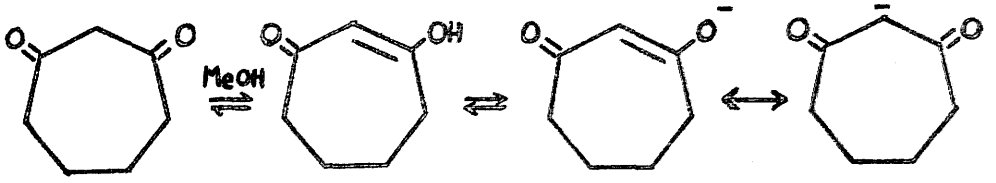
δ						Assignment
Dione alone	Dione in Methanol	Dione in Methanol + drop OH^-	Dione in Carbon Tetrachloride	Dione in Carbon Tetrachloride after deuteration	Dione in Deutero-chloroform	
	4.25		4.23 (w)		4.2 (v.w.)	
3.69	3.76	3.81 (b,w)	3.51 (s)	3.51 (t)	3.60	
2.58	2.61	2.64	2.54	2.54	2.60	
1.80	2.01	2.01	2.05	2.05	2.05	

by deuterium is rapid, and, because of the acidity of these compounds, goes through the anion XXXIIIa.

a b

(XXXIII)

Comparison of the nuclear magnetic resonance spectrum of pure cycloheptane-1,3-dione with that of a methanolic solution, showed a new peak in the latter at δ 4.12 not attributable to methanol. Addition of a trace of alkali caused replacement of this peak by a broad signal, consistent with a rapid exchange system of the type $-O^- \rightleftarrows -OH$. This peak was lost on deuteration and may therefore be attributed to the enolic proton formed on enolisation of cycloheptane-1,3-dione.



(I, R=H)

From the properties of cycloheptane-1,3-dione (see General Introduction - Table I) it is evidently unlike the C_4, C_5 and C_6 cyclic β-diketones.

In the infrared, both thin film and carbon tetrachloride solution spectra of cycloheptane-1,3-dione showed almost complete lack of

enolic absorption, and the carbonyl functions appeared as sharp twin peaks at 1728 and 1704 $cm.^{-1}$. In ethanol, ultraviolet absorption [$\lambda_{max.}$ 2650 Å. (ϵ 3440)] indicated only weak enolisation, while a solution in carbon tetrachloride was almost transparent. Furthermore, cycloheptane-1,3-dione (pK_a 8.64) is a considerably weaker acid than cyclohexane-1,3-dione.

Partial 'trans-fixing' was also demonstrated by the chemical properties of cycloheptane-1,3-dione, as it gave no colouration with ferric chloride and did not form a copper complex on shaking with copper acetate. Unlike cyclohexane-1,3-dione and dimedone, however, it gave no solid derivative with formaldehyde or benzaldehyde. Cycloheptane-1,3-dione was found to undergo very rapid hydrolytic fission by refluxing dilute sodium hydroxide to give 6-oxoheptanoic acid, identified as its semicarbazone by direct comparison with the corresponding derivative of authentic acid prepared by oxidation of 2-methylcyclohexanone with chromium trioxide.[110]

Comparative experiments were conducted to examine the rates of hydrolysis of cycloheptane-1,3-dione, cyclohexane-1,3-dione and acetylacetone under acidic and basic conditions. In each case, a solution of the dione in a fixed volume of water was treated with an equal volume of 6N sodium hydroxide or 6N hydrochloric acid, and allowed to stand at room temperature.

Aliquots were taken at intervals, diluted to standard volume with ethanol and the ultraviolet absorption intensity recorded.

Cyclohexane-1,3-dione, a '<u>trans</u>-fixed' β-diketone showed no variation in absorption intensity after fifteen days in either acid or base under these conditions, thus exhibiting the stability of the anion and oxonium cation of the vinylogous acid.

Acetylacetone, an open chain β-diketone, was similarly unaffected in acid but in alkali the absorption intensity had fallen to half its original value in two hours, and to zero in twenty-four hours. The hydrogen bonded chelate of acetylacetone is disrupted in alkali but is stable in acid.

The instability of cycloheptane-1,3-dione in acid was shown by the reduction of the extinction coefficient to two-thirds of its original value in twelve days at room temperature. While at 100° neglibible intensity resulted in two hours. In base, cycloheptane-1,3-dione showed a rate of hydrolysis intermediate between that of cyclohexane-1,3-dione and acetylacetone, the absorption intensity being halved in seven hours.

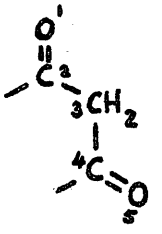
The most striking difference between the cyclic C_6 and C_7 β-diketones is shown by their behaviour towards ethanolic sodium ethoxide. In Section II, one of the reaction products obtained by cyclisation of ethyl 6-oxo-3-phenylheptanoate with sodium ethoxide was identified as 2-acetyl-5-phenylcyclopentanone, and

a mechanism for its formation postulated ring fission of the originally produced 4-phenylcycloheptane-1,3-dione, followed by recyclisation. Corroboration of this theory was sought by examining the effect of sodium ethoxide on cycloheptane-1,3-dione under similar conditions. Accordingly, cycloheptane-1,3-dione was refluxed with sodium ethoxide for two hours, acidified and extracted with ether. The extract was shaken with copper acetate to give a copper salt, which on hydrolysis gave an isomeric β-diketone, shown to be identical in all respects to 2-acetylcyclopentanone by direct comparison with an authentic sample. The postulated ready conversion of cycloheptane-1,3-diones to 2-acylcyclopentanones was thus verified.

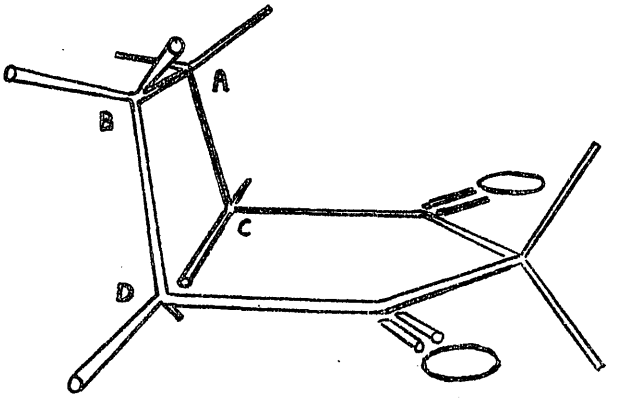
The foregoing facts demonstrate that cycloheptane-1,3-dione does not have characteristics typical of '<u>trans</u>-fixed' cyclic β-diketones. Furthermore, its instability towards base explains the failure of earlier attempts to prepare it by base catalysed cyclisations.[114]

An examination of a molecular model of cycloheptane-1,3-dione provides a rationalisation for the divergence of its properties from those of true '<u>trans</u>-fixed' β-diketones, illustrated by its lack of enolisation, as shown by spectral measurements, and by low acidity. In acyclic '<u>trans</u>-fixed' β-diketones and cyclic β-diketones with four-, five-, and

six-membered rings, the five atoms of the functional group (XXXIV) are coplanar. In the more mobile seven-membered ring the conformation required for coplanarity (XXXV) is highly



(XXXIV)



(XXXV)

strained, and involves eclipsing at carbon atoms A and B and a 1,4-interaction at carbon atoms C and D. In the strain-free conformations the five centres are not coplanar.

In the enol, the effect of introducing a double bond into the ring must be considered. House and Wasson[54] have previously mentioned the instability of a double bond in a seven-membered ring, and the instability of the conjugated enone system in a ring of this size has already been demonstrated in Section IIIb . A conjugated system derives its stability from the delocalisation of its π-electrons, which is at its greatest when the centres involved are coplanar. When coplanarity is impossible there is no driving force for enolisation of a

β-diketone, and in seven-membered rings coplanarity of the conjugated enone system introduces Pitzer strain. The tendency for enolisation to give a conjugated system is thus reduced, though enolisation to give a non-conjugated enone system may still occur. As the anions formed from cycloheptane-1,3-dione are not coplanar, and are less stabilised by delocalisation, it is less acidic than its smaller ring analogues.

The ready interconversion of αβ- and βγ-enones found in seven-membered rings (Section IIIb), is likely to continue in larger rings, where coplanarity will again introduce strain. It is therefore probable that the macrocyclic unsaturated ketones which Leonard and Owens hydrobrominated[68] were not the pure conjugated enones (as the ultraviolet absorption implies). Their failure to obtain β-bromoketones and from these the β-diketones, was therefore predictable.

The properties of cycloheptane-1,3-dione and its derivatives, prepared as above, are in full agreement with those recently reported by Eistert, Haupter and Schank.[53] Contrary to previous reports, however, cycloheptane-1,3-dione may be stored in a stoppered vessel at 0° without decomposition.

EXPERIMENTAL

1,3-Di(carboxymethylene)cyclohexan-2-one (XIII)

A solution of tartaric acid (27 g.) in water (54 ml.) was added to a suspension of sodium metaperiodate (38 g.) partially dissolved in concentrated sulphuric acid (3.6 ml.) and water (220 ml.), while cooling in an ice-bath. The mixture was shaken at room temperature for 1 hr. Freshly distilled cyclohexanone (17.5 g.) was added to the now milky suspension, followed by aqueous sodium hydroxide (27 g. in 450 ml.) and finally ethanol (450 ml.). The whole was stirred at room temperature for 20 hr., and then warmed to 60° for 10 mins. On cooling, the solution was washed with chloroform, acidified, and ether extracted. The extracts were washed with sodium thiosulphate, water and dried. Evaporation gave 1,3-di(carboxymethylene)cyclohexan-2-one (3.80 g.; 10%) (Found: C,56.9; H,4.8. $C_{10}H_{12}O_5$ requires C,57.1; H,4.8%), $\lambda_{max.}$ 2920Å. (ϵ 6500), which recrystallised from light petroleum - ethyl acetate as ill-defined yellow crystals, m.p. 195-198°, $\nu^{nujol}_{max.}$ 3400-2400, 1695 (COOH), 1670 (conj. C = O), 1615, 1600 (double bond), 950, 915 and 895 $cm.^{-1}$, $\lambda_{max.}$ 2950 Å. (ϵ 7,000) (Found: C,57.0; H,5.05%) A red colouration was obtained with tetranitromethane.

The acid gave no S-benzylthiuronium salt and the p-nitrobenzyl ester was an oil.

Shaking the acid with cyclohexylamine in ether gave an

amorphous salt, m.p. 155-159°, from which the acid could be regenerated with mineral acid.

1,3-Di(carboxymethyl)cyclohexan-2-one (XIV).

Crude 1,3-di(carboxymethylene)cyclohexan-2-one (0.844 g.) in alcohol (10 ml.) was hydrogenated over 10% palladium-charcoal. The hydrogen uptake was only two-thirds of that calculated. On filtration and evaporation of solvent, the residue was washed with ether to leave 1,3-di(carboxymethyl)cyclohexan-2-one, which recrystallised from light petroleum-ethyl acetate as fine white needles, m.p. 185-188°, (lit.,[97] m.p. 188°), $\nu_{max.}^{nujol}$ 3400-2400 (broad carboxyl), 1700, and 1690 (ketone and carboxy C = O), 915 and 720 $cm.^{-1}$, $\lambda_{max.}$ 2900 Å.(ϵ 140), (Found: C,55.65; H,6.65. Calc. for $C_{10}H_{14}O_5$: C,56.05; H,6.6%) This compound gave no colouration with tetranitromethane.

Epoxidation of 1,3-di(carboxymethylene) cyclohexan-2-one.

A stirred solution of 1,3-di(carboxymethylene)cyclohexan-2-one (0.553 g.) in methanol (10 ml.) and 30% hydrogen peroxide (4 ml.) was treated with 6N sodium hydroxide (4 ml.) while cooling in an ice-bath. The mixture was stirred overnight, diluted with water, and washed with ether. The aqueous residue was acidified and subjected to continuous ether extraction for 36 hr. On drying and evaporation of the extract a pungent smelling oil was obtained (0.530 g.) which solidified on standing

at 0°, $\nu_{max.}$ 3600-2400 (acidic hydroxyl), 1720-1680 with shoulder at 1600 $cm.^{-1}$ (extremely broad complex carbonyl), $\lambda_{max.}$ 2800 Å. [ϵ 265 (based on M.Wt. 242)].

This compound could not be crystallised and decomposed on warming even under reduced pressure to give a brown tar. No simple carbonyl or acid derivatives were obtained. With 2-amino-2-methylpropanol a salt was formed which decomposed on contact with air.

The epoxidation product (0.172 g.) was treated in ether with diazomethane, and the product dried and distilled (125-140°/ 0.4 mm.) to give a mixture of esters (0.168 g.). The esters were chromatographed on alumina (15 g., Grade III) and a measure of separation into two major components obtained. Neither of these esters exhibited ultraviolet absorption.

Lead tetra-acetate.[98]

Red lead (600 g.) was added to a stirred mixture of glacial acetic acid (1080 g.) and acetic anhydride (360 g.), while the solution temperature was maintained at 50-60°. On completion of addition, stirring was continued overnight at room temperature. The lead tetra-acetate was filtered, washed repeatedly with glacial acetic acid, and recrystallised from this solvent as white needles, which were kept damp with glacial acetic acid to minimise decomposition.

Ethyl hemiacetal of ethyl glyoxylate[99] (VIII)

Lead tetra-acetate (120 g. - still moist with glacial acetic acid) was added to a stirred solution of diethyl tartrate (60.9 g.) in benzene (300 ml.). Stirring was continued overnight and lead salts removed by filtration. The filtrate was evaporated to small volume (ca.50 ml.), absolute alcohol (150 ml.) added, and the solution fractionated through a column. Redistillation gave the ethyl hemiacetal of ethyl glyoxylate (17.9 g.; 21%) as a clear oil, b.p. 50-55°/20 mm. (lit.[99]; b.p. 54-55°/16 mm.), n_D^{20} 1.4192.

Ethyl 2-oxocyclohexylideneacetate[94] (X)

A sealed Carius tube containing cyclohexanone (15.4 g.) and ethyl glyoxylate hemiacetal (11.1 g.) was heated in a furnace at 200° for three hours. After removal of unchanged starting materials at reduced pressure, the residue was distilled in vacuo to give the crude condensation product (5.35 g.), b.p 145-160°/20 mm. A considerable amount of non-volatile material remained.

Potassium bisulphate (4 g.) was added to the distillate and the mixture heated for 30 min. (at 10 mm. pressure) on a steam bath. The bisulphate was filtered, washed with ether, and the ethereal solution dried and distilled to give ethyl 2-oxocyclohexylideneacetate (3.35 g.; 24%) as a colourless oil,

b.p. 145-147°/14 mm. (lit.,[94] b.p. 132°/12 mm.) $\nu_{max.}$ 1725 (ester), 1695 (ketone), 1660 (conjugated C = O), 1600 (double bond) and 990 $cm.^{-1}$.

This compound gave an intense colouration with tetranitromethane.

2-Oxocyclohexylideneacetic acid (V, R = COOH)

Ethyl 2-oxocyclohexylideneacetate (1.29 g.) was refluxed for 15 min. with a 1:1 mixture of conc. hydrochloric and glacial acetic acids (5 ml.). The cooled solution was diluted and extracted with ether, the extract yielding unhydrolysed ester (0.120 g.). Evaporation of the acidic aqueous residue left a red-brown solid which, on extraction with boiling light petroleum, gave 2-oxocyclohexylideneacetic acid (0.323 g.; 29%) as white plates, m.p. 99-100°, (lit.,[93] m.p. 104-105°), $\nu_{max.}$ 3300-2500 (carboxyl), 1698 (CO of carboxyl), 1665 with shoulder at 1610 (conj. C=O), 990, 940-900 (b) and 748 $cm.^{-1}$ $\lambda_{max.}$ 2330 Å. (ϵ 9880) [lit.,[93] for *cis*, $\lambda_{max.}$ 2330 Å. (ϵ 9333)] N.M.R.: δ 10.09 (s, 1 proton) -COOH, δ 6.9 (b, 1 proton) $>C = CH-CO$, δ 3.23 (b, 2 protons) CH_2CH_2CO, δ 2.35 (v b, 6 protons) CH_2. (Found: C, 62.3; H, 6.7. Calc. for $C_8H_{10}O_3$: C, 62.3; H, 6.55%)

Epoxidation of 2-oxocyclohexylideneacetic acid.

A stirred solution of 2-oxocyclohexylideneacetic acid (0.430 g.) in methanol (8 ml.) was treated with 30% hydrogen peroxide (1.8 ml.) followed by 6N sodium hydroxide (2.8 ml.),

while cooling in an ice-bath. After stirring overnight, the mixture was diluted with water and washed with ether. The aqueous residue was acidified, extracted with ether (5x), and the extracts washed with sodium bicarbonate. Acidification of the bicarbonate washings, and extraction with ether (5x) gave, on drying and evaporation, a pale yellow oil (0.099 g.), which showed acidic hydroxyl and broad carbonyl absorption in the infrared.

This acid (99 mg.) in ether was treated with an ethereal solution of 2-amino-2-methylpropanol to give the amine salt (128 mg.), from which the acid (62 mg.) was regenerated by shaking with mineral acid.

The amine salt could not be purified by recrystallisation, so purification was attempted by repeated salt formation and regeneration of the acid. After four formations the salt was obtained as a white powder, m.p. 131-134°. Analytical data were unsatisfactory (Found: (a) C,53.9; H,8.0; N,5.7. (b) C,54.1; H,8.1. Calc. for $C_{12}H_{21}O_5N$: C,55.6; H,8.15; N,5.4%).

The acid (22 mg.) was regenerated from the salt as an apparently homogeneous (thin layer chromatography) yellow oil, $\nu_{max.}$ 3500-2400, 1710-1680 with weak shoulder at 1600 $cm.^{-1}$ $\lambda_{max.}$ - nil.

Cyclohept-2-enone and cyclohept-3-enone.

0.5 ml. samples of cycloheptenone (b.p. 182-184°; $n_D^{20.5}$ 1.4910) from 'tropidine'[103] were eluted on a Gas Chromatography Ltd. preparative column, using 20% apiezon M on celite as column packing. Separation was effected using a column temperature of 100°; gas inlet pressure 18 mm. (mercury); and gave finally, small yields of:-

(a) Cyclohept-2-enone (XVIIIa) as a colourless oil, b.p. 76°/18 mm., $\lambda_{max.}$ 2280 Å. (ε 10,060), $\lambda_{max.}^{hexane}$ 2200 Å. (ε 10,700). $\nu_{max.}$ 3030 (weak enolic OH), 1670-1655 (conjugated C = O), 1635 (double bond), 890, 820, 790 and 690 $cm.^{-1}$ (cis-double bond) (Found: C,75.9; H,9.3. Calc. for $C_7H_{10}O$: C,76.3; H,9.15%).

The ketone (0.235 g.) in ethanol was hydrogenated in the presence of palladium, to give cycloheptanone, $\nu_{max.}$ 1705 $cm.^{-1}$, $\lambda_{max.}$ only weak carbonyl absorption. Treatment of the reduction product in ethanol with Brady's reagent gave the 2,4-dinitrophenyl-hydrazone of cycloheptanone, which recrystallised from ethyl acetate as yellow prisms, m.p. 148-151°, alone or admixed with an authentic specimen.

(b) Cyclohept-3-enone (XVIIIb), as a colourless oil, b.p. 180-181° $\lambda_{max.}^{hexane}$ only weak carbonyl absorption, $\nu_{max.}$ 1704 (unconjugated C = O in seven membered ring), 1660 (double bond), 995, 790 and 690 $cm.^{-1}$ (cis-double bond) (Found: C,75.9; H,8.9. Calc. for $C_7H_{10}O$: C,76.3; H,9.15%). Catalytic hydrogenation of the ketone as above and treatment with Brady's reagent gave the

2,4-dinitrophenylhydrazone of cycloheptanone as yellow plates, m.p. 148-151°, alone or admixed with an authentic specimen.

The mixed cycloheptenones [b.p. 76-79°/14 mm., n_D^{16} 1.4870, $\lambda_{max.}$ 2270 Å. (ϵ 3,800)] were also prepared from cycloheptanone, according to Treibs and Grossmann.[105] Treatment of an ethanolic solution of the isomers with Brady's reagent and chromatography on silica gave as the major product, the 2,4-dinitrophenylhydrazone of cyclohept-2-enone, which recrystallised from ethanol as red-orange plates, m.p. 131-134° (lit.,[100] m.p. 122°,[105] 141°), $\lambda_{max.}^{CHCl_3}$ 3710 Å. (ϵ 24,070) (Found: C, 53.4; H, 5.15; N, 19.2. Calc. for $C_{13}H_{14}N_4O_4$: C, 53.8; H, 4.85; N, 19.3%).

The mixture was separable on an analytical Pye Argon Column (1.2 m x 4 mm.) using a 10% apiezon L packing at 95°. For preparative work separation was achieved on a Pye Argon column (1.2 m x 10 mm.), using 25% apiezon L on celite at a tempterature of 105°, argon pressure 4 lb./in², to furnish pure cyclohept-2-enone, $\lambda_{max.}$ 2270 Å. (ϵ 11,040), $\nu_{max.}^{CS_2}$ 3020, 1674, 1662, 896, 819, 810, 787 and 689 $cm.^{-1}$

Isomerisation of cyclohept-2-enone.

A solution of cyclohept-2-enone (1.1 mg.) in ethanol (25 ml.) was treated with a drop of sodium hydroxide solution (5 N) and allowed to stand at room temperature. Aliquots were taken periodically and their ultraviolet spectrum recorded.

The extinction coefficient at $\lambda_{max.}$ 2280 Å. (originally 11,040) fell within three hours to an equilibrium value of 1,000.

3,4,5-Trimethoxybenzoic acid. (XXVIII, R = H)

Dimethyl sulphate (300 ml.) was added dropwise to a cooled efficiently stirred, solution of gallic acid (125 g.) in acetone (3 l.), followed by portionwise addition of A.R. potassium carbonate (500 g.). The mixture was stirred and refluxed overnight. On cooling, the potassium carbonate was removed by filtration and the filtrate evaporated until the acetone was almost completely removed. The residue was diluted, extracted with ether, and the extracts washed with dilute sodium carbonate and water. Drying (Na_2SO_4) and evaporation gave methyl 3,4,5-trimethoxybenzoate (146 g.), m.p. 79-81° (unrefined) (lit., m.p. 85°).

The crude ester was refluxed overnight with 10% aqueous sodium hydroxide, and the oooled solution washed with ether before acidification and extraction with chloroform. The chloroform extracts were washed with dilute acid, dried (Na_2SO_4) and evaporated to give 3,4,5-trimethoxybenzoic acid (126 g., 81%), which crystallised from water as fine white needles, m.p. 172-174° (lit.[111], m.p. 167-168°).

1,4-Dihydro-3,5-dimethoxybenzoic acid.[109] (XXIX)

Liquid ammonia (1.5 l.) was added to a solution of 3,4,5-trimethoxybenzoic acid (31.6 g.) in ethanol. While agitating this solution with a Herschberg stirrer, sodium (18 g.) was added in small portions, and stirring continued a further 15 min. before addition of ammonium chloride (75 g.). The ammonia was allowed to evaporate overnight, the residue taken up in ice-water (2 l.) and the solution extracted with methylene chloride after each addition of small portions (ca.5 ml.) of 6N hydrochloric acid, until the aqueous phase was finally acidic to Congo Red. The organic extracts were washed with water containing a trace of acid, dried ($MgSO_4$) and evaporated to small bulk. By trituration of the residue with a small quantity of ether, white plates of 1,4-dihydro-3,5-dimethoxybenzoic acid (18.9 g., 69%), m.p. 98-101°, were obtained (lit.,[109] m.p. 105°).

1,4-Dihydro-3,5-dimethoxybenzyl alcohol[108] (XXX).

A solution of 1,4-dihydro-3,5-dimethoxybenzoic acid (18.9 g.) in sodium-dried tetrahydrofuran (90 ml.) was cautiously added to a vigorously stirred suspension of lithium aluminium hydride (8.6 g.) in ether (600 ml.), under nitrogen, and the mixture stirred and refluxed for 1½ hr. On cooling, excess lithium aluminium hydride was destroyed by addition of ethyl acetate, and the solution washed with dilute sodium hydroxide and water. The ether residue was dried and distilled to give

1,4-dihydro-3,5-dimethoxybenzyl alcohol (13.9 g.; 80%) as a colourless oil, b.p. 99-104°/ 0.3 mm. (lit.,[108] b.p. 93-95°/ 0.2 mm.).

Tosylation and solvolysis of 1,4-dihydro-3,5-dimethoxybenzyl alcohol: 1,3-Dimethoxycycloheptatriene[108] (XXIV).

Optimum yields in this preparation were obtained using freshly distilled pyridine which had been dried by refluxing over barium oxide, and p-toluenesulphonyl chloride freshly recrystallised from light petroleum.

1,4-Dihydro-3,5-dimethoxybenzyl alcohol (13 g.) in pyridine (50 ml.) was added to an ice-cooled solution of p-toluenesulphonyl chloride (20 g.) in pyridine (120 ml.), and the mixture stirred under nitrogen for 5 hr. On addition of ice-water, the tosylate (XXVI) separated as an oil which solidified on standing. After filtration and washing with water, the still damp tosylate was immediately solvolysed by warming in aqueous pyridine for 30 min. The bulk of the pyridine was then removed *in vacuo* at room temperature, and the residue diluted with water and extracted with ether. The extracts were washed with dilute sodium carbonate, 6N hydrochloric acid, water and dried before evaporation to leave a brown oil. Distillation gave an impure mixture of 1,3-dimethoxycycloheptatrienes (3.1 g., 27%) as a colourless oil, b.p. 68-70°/0.2 mm. (lit.[108] b.p. 56-58/

0.1mm.) which rapidly darkened on standing, $\nu_{max.}$ 3000 (w, hydroxyl), 1710 (w), 1650 (w), 1600, 1000, 900, 870, 830, 805 and 770 $cm.^{-1}$, $\lambda_{max.}$ 2420 and 2880 Å. (ϵ 1890 and 7050 respectively) [lit.,[108] $\lambda_{max.}$ 2880 Å. (ϵ 9085)].

1,3-Dimethoxycycloheptadiene (XXXI).

A solution of 1,3-dimethoxycycloheptatriene (1.756 g.) in absolute alcohol was hydrogenated using 10% palladium-charcoal as catalyst. After addition of 1.05 mol. hydrogen, the solution was filtered, evaporated, and the residue taken up in ether and dried (Na_2SO_4). Distillation gave an impure mixture of 1,3-dimethoxycycloheptadienes (1.531 g.; 86%) as a colourless oil, b.p. 68-70°/0.2 mm., $\nu_{max.}$ 2950 (w hydroxyl), 1695 (w), 1640, 1600, 990 and 870-820 $cm.^{-1}$, $\lambda_{max.}$ 2550 Å. (ϵ 6160) and $\lambda^{OH^-}_{max.}$ 2880 Å. (ϵ 15,780).

The distillate, on standing overnight with Brady's reagent gave a 2,4-dinitrophenylhydrazone which recrystallised from alcohol as yellow needles, m.p. 174-177° (Found: (a) C,46.9; H,4.01; N,23.2: (b) C,47.05; H,3.95; N,22.95. Calc. for $C_{19}H_{18}N_8O_8$*: C,46.9; H,3.7; N,23.0%).

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* Molecular formula of bis-2,4-dinitrophenylhydrazone of cycloheptane-1,3-dione.

Cycloheptane-1,3-dione (I, R = H)

1,3-Dimethoxycycloheptadiene (1.152 g.) was stirred in aqueous oxalic acid (5 g. in 30 ml. water), with the temperature held at 40-50° for 4 hr. The cooled solution was washed with hexane (2x) before extraction with chloroform. The chloroform extracts were washed with water, dried (Na_2SO_4) and distilled to give cycloheptane-1,3-dione (0.807 g.; 85%) as a colourless oil, b.p. 119-122°/15 mm., $\nu_{max.}^{CCl_4}$ 3415 (weak, enol), 1728, 1704 (strong, twin C = O), and 929 $cm.^{-1}$, $\lambda_{max.}$ 2650 Å. (ϵ 3440), $\lambda_{max.}^{OH^-}$ 2880 Å. (ϵ 24,060) and $\lambda_{max.}^{CCl_4}$ transparent, N.M.R. see Table III and text, pK_a 8.64 (by titration with tetramethylammonium hydroxide) (Found: C,66.75; H,7.8. Calc. for $C_7H_{10}O_2$: C,66.65; H,8.0%).

Cycloheptane-1,3-dione-bis-2,4-dinitrophenylhydrazone.

Addition of cycloheptane-1,3-dione (0.104 g.) to Brady's reagent gave an immediate yellow precipitate (0.156 g.), m.p. 191-196°, which was eluted twice from a silica column with benzene-chloroform (3:1). Recrystallisation from a mixture of chloroform and ethanol gave the bis-2,4-dinitrophenylhydrazone of cycloheptane-1,3-dione, as orange-yellow needles, m.p. 208-212° (Found: C,46.7; H,3.95; N,23.1. Calc. for $C_{19}H_{18}N_8O_8$: C,46.9; H,3.7; N,23.0%).

Cycloheptane-1,3-dione dioxime.

Hydroxylamine hydrochloride (0.630 g.) was dissolved in water (4 ml.), and the solution buffered to pH5 with sodium acetate, before addition to cycloheptane-1,3-dione (0.083 g.) in a few drops of water. Warming on a water bath for 5 min. and cooling gave colourless crystals (0.73 g.), m.p. 156-161°, which recrystallised from small portions of methanol to give the bis-oxime of cycloheptane-1,3-dione as colourless prisms, m.p. 164-166° (Found: C,54.15; H,7.9; N,17.95. Calc. for $C_7H_{12}N_2O_2$: C,53.85; H,7.75; N,17.95%).

Hydrolysis of cycloheptane-1,3-dione.

Cycloheptane-1,3-dione (0.094 g.) was warmed on a steam bath, with 10% sodium hydroxide (5 ml.) for 2 hr. On cooling, the solution was washed with ether, acidified and extracted with ether overnight. The extracts were washed, dried (Na_2SO_4) and evaporated to give 6-oxoheptanoic acid (0.110 g.) which sublimed (125°/0.1 mm.) as a viscous oil, identical in the infrared with an authentic specimen.

The sublimate gave the semicarbazone of 6-oxoheptanoic acid as white needles from ethanol, m.p. 142-144°, either alone or admixed with an authentic specimen. (Found: C,47.65; H,7.15; N,21.2. Calc. for $C_8H_{15}N_3O_3$: C,47.75; H,7.5; N,20.9%).

Semicarbazone of 6-oxoheptanoic acid.[110]

A mixture of chromium trioxide (15.6 g.) and conc. sulphuric acid (22.4 g.) was added over 5 hr. to a stirred solution of 2-methylcyclohexanone (10.6 g.) and glacial acetic acid (2 ml.), and stirring continued for a further 2 hr. Water was added, and unchanged 2-methylcyclohexanone steam distilled from the system. Excess ammonium sulphate was added to the still hot solution, which was ether extracted on cooling. The extracts were washed with ammonium sulphate in dilute sulphuric acid, dried and distilled to furnish 6-oxoheptanoic acid (5.76 g.; 42%) as an oil, b.p. 122-125°/0.1 mm., which solidified on cooling to give a low-melting white solid (lit.,[112] m.p. 34-35°).

Treatment as before gave an immediate precipitate of the semicarbazone of 6-oxoheptanoic acid, which recrystallised from ethanol as white needles, m.p. 144-145° (lit.,[113] m.p. 144°).

Reaction of cycloheptane-1,3-dione with sodium ethoxide: 2-Acetylcyclopentanone.

Cycloheptane-1,3-dione (0.402 g.) was added to a refluxing solution of sodium ethoxide [from sodium (0.09 g.) in ethanol (1.8 ml.)], and refluxing continued for 2 hr. The cooled solution was acidified with glacial acetic acid diluted with water, and extracted with ether. The ethereal extracts, after washing, were shaken with an aqueous solution of copper acetate.

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