THE ENOLISATION OF SOME DIAROYLMETHANES AND THE ACYLATION OF THEIR METAL CHELATES

MICHAEL GERARD MURRAY

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SUMMARY

A study of the structures of the isoxazoles derived from a series of diaroylmethanes has shown that the enolic form of these diketones contains a high degree of electron delocalisat within the chelated ring. Partial charge localisation is effected by aryl substituents whose inductive and mesomeric effects act in the same direction, and one carbon-oxygen bond exclusively has 'carbonyl character'. When the inductive and mesomeric natures of the substituents are mutually opposed the enol behaves as a mixture of tautomers, and both carbon-ox bonds have double bond character.

In an extension of a previous investigation of the mechanis of acylation of β-diketone metal chelates, the importance of t electronic nature of the ligand has been clarified. As the electron-affinity and acidity of the parent diketone increases, so the proportion of C-substitution occurring in the acylation the chelates, is found to decrease. The observations have con that this reaction proceeds by coordination of the acid halide the metal of the chelate, permitting the formation of cyclic transition intermediates which yield the triketone and ester products. When the metal is incapable of being coordinated by the reagent, reaction proceeds by an ionic process, and a high proportion of ester results, which is relatively independent of the ligand substituents.

Reaction of the diketones with benzoyl chloride in pyridine

yielded only one ester, whereas two isomers are theoretically possible. The same single product was isolated from the reactions of the diketone chelates. This selectivity of atta has been attributed to the participation of the enolate anion in the direct esterification of the diketone, and to asymmetr in the metal-oxygen bonding in the chelates. Physical eviden of an interaction between pyridine and the diketones has been observed, and this is believed to give rise to the anion in t reaction. The more stable anion, dictated by that conjugatio which gives the greater loss in potential energy, is exclusiv formed. Previous evidence has discounted the possibility of an ionic esterification of the chelate, and bond asymmetry, a least in the transition stage of the reaction, is envisaged a an explanation of the selectivity of the position of attack.

THESIS

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CONTENTS

INTRODUCTION

The research reported in this thesis was initially aimed at the extension of recent investigations into the acylation reactions of the metal complexes of β-diketones. Specifically, it was intended to study the control exercised over these reactions by the electronic character of the parent ligand. For this purpose, a series of mono-substituted dibenzoylmethanes and their chelates were prepared and examined.

One product of these reactions was the enol ester of the diketone, which was formed exclusively in one of the two possible isomeric structures. It was expected that this structure would be related to the enolic form of the diketone and to the nature of the substituent. When the methoxyl group was present, the observed behaviour reversed that of the other substituents used (methyl and nitro) in relation to the enol structure, as shown by isoxazole formation. The direction of enolisation of a series of these diketones was therefore determined by preparing and identifying their isoxazoles, and the relationship between the enol and the enol ester was examined in relation to the nature of the substituent.

This report is therefore presented in two sections dealing, respectively, with the metal chelate reactions and with the enolisation and esterification of the parent β-diketones.

CHAPTER I

METAL CHELATES

Structure of the Chelates.

In the field of co-ordination chemistry, the term 'chelate' is used to describe the cyclic compound formed by the linkage of both ends of a chain of atoms to a central metal atom. The name arises from the claw-like 'grip' of the ligand to the metal.

The size of such a chelate ring is variable, but the most stable compounds enclose five or six atoms. Where the system contains no unsaturation, the five-membered ring is most favoured, since it imposes least strain on the normal bond angles; and for a similar reason, unsaturated chelates contain mainly six-membered rings.

Oxygen and nitrogen, by virtue of their lone pairs of electrons, are the atoms most commonly found to co-ordinate in such systems. Typical ligands are the amino- and hydroxy-carboxylic acids, diamines, dicarbonyl compounds and similar systems.

The reversible formation of a chelate may be represented by the general equation

$$M^{n+} + nA^{-} \rightleftharpoons MAn$$

where M is a metal of co-ordination number 2n, and A^{-} represents the anion of the chelating ligand. The stability constant K of the chelate is given by

$$K = \frac{[MAn]}{[M^{n+}]\,[A^{-}]^{-}}$$

Comparison of the experimental values of K for various systems has given information on some of the factors which control chelate formation.

In systems with a high degree of ionic bonding, it is found that the chelate stability increases with the charge density of the metal ion, but decreases with increasing ionic radius[1]. This does not hold for chelates with highly covalent linkages, and can be used to distinguish the two extreme cases.

A similar relationship is found between chelate stability and the ionisation potential of the metal (the 'last' potential to give the appropriate ion) as in the complexes of the first transition series:

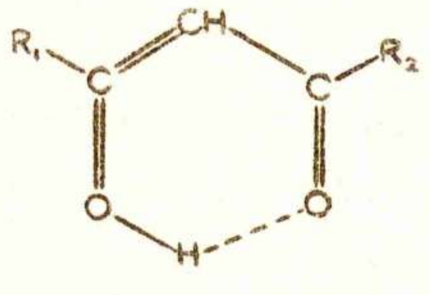
$$\mathrm{Mn} < \mathrm{Fe} < \mathrm{Co} < \mathrm{Ni} < \mathrm{Cu} > \mathrm{Zn}$$

This series holds true for the divalent complexes, and is in the same order as the second ionisation potentials of the metals[2].

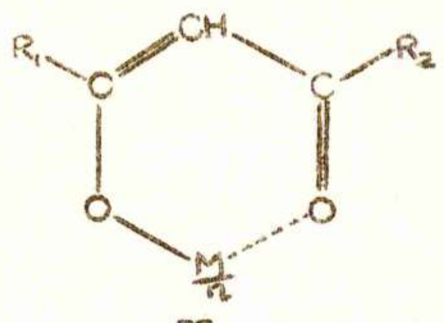
A corresponding increase in stability with increasing basicity in the co-ordinating atoms of the ligand was observed by Calvin[3], who showed a linear relationship between K and the pK_a of the chelating agent.

These observations are all in agreement with simple electrostatic principles, at least to a qualitative extent.

The enolic modification (I) of the β-diketone system is particularly suitable for chelate formation.



I



II

Replacement of the enolic proton by a metal atom, and co-ordination of the second carbonyl-oxygen atom to the metal, gives a six-membered ring containing a conjugated double-bond system (II).

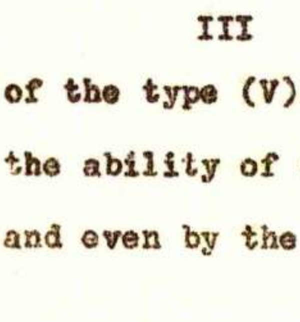
Werner first suggested that these derivatives were not simple salts, but had a cyclic structure[4], and the accumulating evidence in favour of this view was reviewed by Diehl[5].

The bonds between the metal and the ligand are similar to those of the 'Werner' co-ordination complexes, and vary in nature from highly covalent to highly ionic. The latter are rarely of the pure ionic type, but arise from the electrostatic attraction of the metal ion for the dipoles present in the ligand. This variation in the bond-type is reflected in the physical properties of the chelates, which are sometimes water-soluble typically inorganic substances, but sometimes behave like organic compounds in solubility and stability. Despite the highly inorganic behaviour of some chelates, they generally retain the cyclic structure, and only occasional examples of true 'salts' occur, as in the case of mercury (II) β-diketonates[6].

Infrared spectra of the chelates[7] confirm the cyclic structure, showing carbonyl absorption displaced to the 'chelate carbonyl region', whereas true acyclic compounds, such as the mercuric derivatives, have normal α,β-unsaturated carbonyl absorption frequencies[6].

Some indication of the bond-type may be obtained from the ultraviolet absorption spectra. When covalent bonding is present, the absorption maxima of the parent diketone are bathochromically displaced in the chelate spectrum, whereas ionic compounds have similar spectra to the parent.[8,9]

The simple cyclic structure which Werner proposed for the chelates could not adequately explain the high physical and chemical stability of the compounds, which can frequently be distilled, crystallised or sublimed without decomposition[10,11]. Martell and Calvin[12] suggested that resonance stabilisation by the forms (III) and (IV) would explain these properties, and even considered the possibility of complete benzenoid resonance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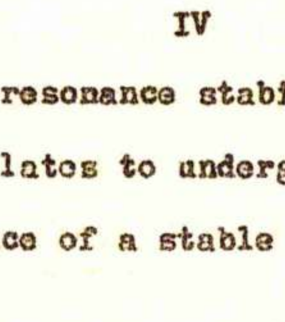
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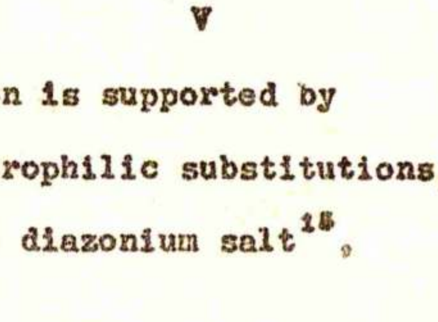
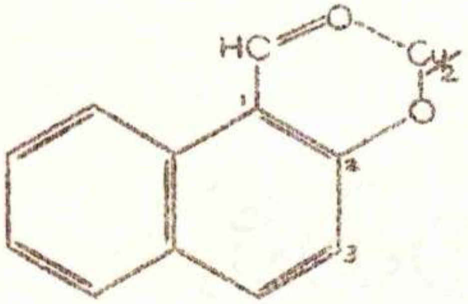
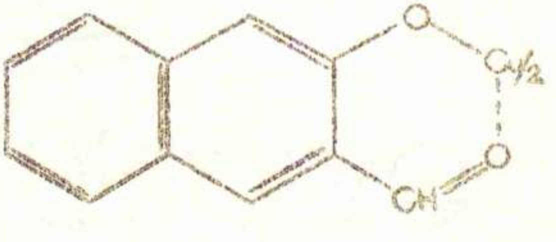

V

of the type (V). Such resonance stabilisation is supported by the ability of some chelates to undergo electrophilic substitutions,[13,14] and even by the existence of a stable chelate diazonium salt[15], all typically aromatic properties. Further evidence for the resonance concept is given by the observed reduction in chelate stability produced by lowering of the carbon-carbon double bond character within the chelate ring. Thus the compound (VI) is found to be much more stable than (VII)[16], since the $C_1 - C_2$ bond in naphthalene has greater double-bond character than the $C_2 - C_3$ bond.

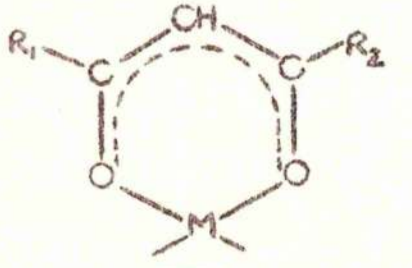


VI

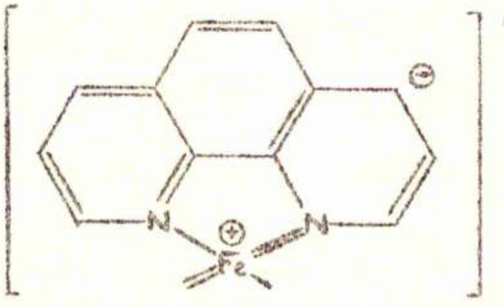


VII

X-ray analyses of β-dicarbonyl chelates[17,18,19] show that the chelate ring is planar, with symmetrical bond lengths. The C-C and C-O bonds have partial double-bond character, but the M-O bond lengths are even greater than normal single-bond lengths. This supports the concept of a partial bond delocalisation such as in (VIII). Some chelates undoubtedly do have some metal-ligand double bond character, such as the ferrous o-phenanthroline complex (IX)[20,21]. This effect arises when the metal atom has



VIII



IX

d electrons available for back donation to vacant orbitals on the ligand, thus giving the usual σ bond some degree of π bond character[16].

The most widely used theoretical approaches to the bonding in chelates have been the Valence Bond Theory, as developed by Pauling[22], and the Ligand Field Theory[23]. By considering the directional and energy characteristics of the ligand and metal atomic orbitals, with the various possible hybridisations and spacial directions, satisfactory explanations of magnetic and stereochemical properties and of absorption spectra and other characteristics, have been obtained.

Chelates of the alkali and alkaline earth metals generally have greater ionic character than the corresponding transition metal complexes. Sidgwick[24] found that some alkali metal chelates were acyclic salts, whereas others were di-covalent cyclic compounds. However, simple solubility criteria are not sufficient evidence for assigning a salt-like structure, since the infrared spectra of many apparently ionic chelates show the presence of a co-ordinated ring. Most of these compounds can be co-ordinated further by hydration or by treatment with suitable solvating media, and many stable tetra- and hexa- covalent complexes have been isolated[24]. This ease of extension of the co-ordination number of the metal has an important bearing on the mechanism of the acylation reactions of the compounds.

The transition metals are especially suitable for complex formation, since they have available the low-energy d orbitals which readily accept electron pairs from a donor-ligand to form covalent linkages. Studies of the stereochemistry and magnetic properties of these chelates, in relation to the directional characteristics of the orbitals and electronic configuration of the metal ion, have given much information on the structures and bonding of the compounds.

Copper has the outer electron configuration $(3s)^2 (3p)^6 (3d)^{10} (4s)^1$, and so the cupric ion could either be $(3s)^2 (3p)^6 (3d)^8 (4s)^1$ or $(3s)^2 (3p)^6 (3d)^9$. Thus, in tetraco-ordinate cupric complexes, the former configuration would form four planar dsp^2 covalent hybrid orbitals, and the latter, four tetrahedral sp^3 covalent hybrids. Also, since ionic bonds are non-directional, a purely ionic copper complex would have the most symmetrical structure viz. tetrahedral. Thus, the planar structures of the copper chelates of acetylacetone, benzoylacetone and others, established by optical studies[25,26], show the covalent nature of the bonding.

The most common co-ordination number of copper is four, but this can generally be increased to five. Thus, copper chelates are readily solvated by pyridine[27] and some Lewis bases[28,29]. Spectroscopic evidence[30] has shown that copper acetylacetonate is readily solvated by heterocyclic bases, and the monosolvate with 4-methylpyridine has been isolated[31].

Gillard and Wilkinson[32,33] have confirmed and extended these observations, and have also shown that when the ligand is sufficiently electron-attracting in nature, as is trifluoroacetylacetone, the copper co-ordination number may be increased to six. This phenomonon must be due to the decreased neutralisation of the charge on the metal, with a consequent increase in electrophilicity.

The divalent nickel ion has the outer electron configuration $(3s)^2\ (3p)^6(3d)^8$. The 3d subshell will normally have the eight electrons arranged as three pairs, with two unpaired in accordance with Hund's rule. Thus, when the ion forms co-ordination complexes, the electrons from the donor will enter the hybrid orbitals formed from the 4s and 4p shells, giving a tetrahedral sp^3 structure. Since the 3d shell contains two unpaired electrons, these complexes are paramagnetic. Alternatively, the nickel ion can fill four of the 3d orbitals with electron pairs, leaving the fifth to combine with the 4s and two of the 4p orbitals as four dsp^2 hybrids, with a planar structure. This arrangement contains no unpaired electrons, and complexes formed from it are diamagnetic. Examples of both these arrangements are found in the nickel complexes.

Mellor and Craig[34] found that several nickel chelates of β-diketones were paramagnetic, and therefore concluded that when nickel was bonded to four oxygen atoms, a tetrahedral, paramagnetic structure would result. However, Cotton[35] has recently found that the magnetic properties of such chelates are dependent on temperature, with a decrease in magnetic moment as the compounds are heated. He has shown that these chelates are trimeric at room temperature, and each nickel atom is bonded to six oxygens, arranged octahedrally. The structure is an sp^3d^2 hybrid, which will be paramagnetic. The monomers[36] are planar and diamagnetic. This explanation is further substantiated by the fact that when the end-groups of the diketone are sufficiently large to prevent molecular association, as in nickel dipivaloylmethide, the chelate is diamagnetic even at room temperature.

The normal nickel co-ordination number of four in its chelates is readily increased to six by the solvating media already described. In general, the paramagnetic complexes are very readily solvated to diamagnetic compounds, and the co-ordinating substance is not easily removed[37]. In contrast, the diamagnetic chelates are less readily solvated, and the products are comparatively easily broken down into the original chelate and solvent[38]. The paramagnetic compounds are apparently more ionic in nature, and the components of the complex undergo rapid exchange in presence of unchelated components[38,39,40]. Diamagnetic chelates have a greater degree of covalency in their bond structures.

Among the transition metals, zinc represents a special case, since it marks the completion of the 3d subshell, and has the outer electron configuration $(3s)^2 (3p)^6 (3d)^{10} (4s)^2$. In the divalent ion Zn^{2+}, it is the 4s electron pair which has been removed, and so no 3d orbitals are available for complexing. Thus, zinc chelates have an sp^3 hybrid bond structure, which is tetrahedral. This absence of low energy d orbitals prevents zinc from increasing its co-ordination number above four, and the chelates do not solvate, which results in a different mechanism of acylation from other chelates. This outer-orbital[38], tetrahedral structure gives zinc complexes greater ionic character[12], by analogy with tetrahedral nickel structures. However, the chelates are more stable and more covalent than those of the alkali series.

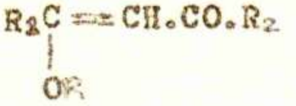
Mercury has a similar outer electronic configuration to zinc, with the same absence of d orbitals. In mercury complexes, however, there is evidence that the structures are acyclic salts[6]. This may be due to the greater ionic radius (1.12 Å) of mercury as compared to zinc (0.83 Å).

In general, therefore, although the stereochemistry and bond-structure of the chelates vary with both metal and ligand, each individual chelate ring is planar, with a delocalised electron system which gives the compound aromatic character. This aromaticity is greatest with ligands of relatively high basicity, and with metals which have d orbitals available for covalent bonding, especially when inner orbital hybridisation is possible.

The Acylation Reaction of the Chelates.

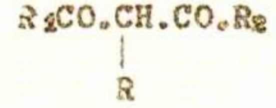
Alkyl or acyl halides attack chelates of β-diketones at both the carbonyl-oxygen and central carbon atoms, to yield the

O- and C- substituted compounds (X) and (XI). The relative yields of the isomeric products can be varied by the use of



$$\underset{\displaystyle OR}{R_1\overset{}{C}} = CH.CO.R_2$$

X



$$R_1CO.\underset{\displaystyle R}{CH}.CO.R_2$$

XI

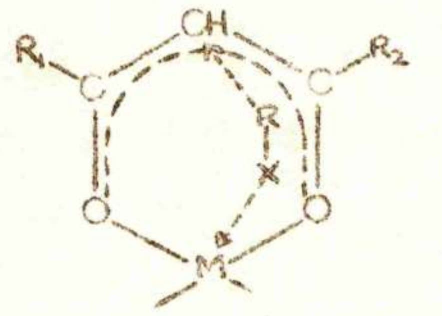
different metals, ligands and reaction conditions.

Most work on these reactions was aimed at the syntheses of C alkylated compounds, and little attention was given to the accompanying enol ethers or esters. The alkali metals were almost invariably employed in the chelates, and a review of these reactions has been made by Brandstrom[41,42]. The proportions of the two products were usually measured in a qualitative manner, and an understanding of the reaction mechanism has only grown slowly.

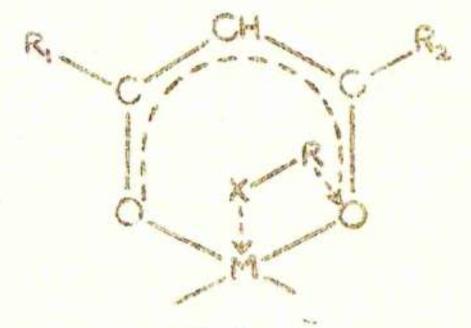
Claisen[43] showed that the C- compound could be produced by isomerisation of the O- isomer, when the metal complex was present as 'catalyst'. He therefore suggested that the enol ether or ester was formed by reaction of the enolate anion, with subsequent partial or complete isomerisation to the C- compound. However, Michael and Carlson[44] demonstrated the formation of C- compound under conditions where this isomerisation would not take place. Michael's suggestion of an addition of the reagent to the chelate double-bond, with separation of the metal halide, could not be substantiated by analogous reaction of the diketone-enol with alkyl or aryl halides.

Arndt and Eisterdt[45] had suggested that the enolate anion had a delocalised charge, resulting in C- substitutuion together with the expected ether or ester. However, C- substitution has never been observed without the presence of the metal ion, and the spectra[46] of enolate anions show no evidence of charge delocalisation. A modification of this theory was proposed by Kornblum[47], who considered that the enolate anion was formed during the reaction transition state, and could thereby have a transient charge delocalisation to an extent determined by the nature of the diketone. Halides of high S_N1 character, i.e. tendency to form carbonium ions, would favour O- substitution, since oxygen would have the greater charge concentration; S_N2 character in the reagent would increase the yield of C- compound.

Brandstrom[41,42] believed that two separate mechanisms existed for the formation of the isomers. Although he favoured the idea of an ionic reaction for production of the O- compound, he also considered that the halide could co-ordinate to the chelate, and would thereby react to form the C- isomer. This was the first theory to take account of the role of the metal ion in the reaction. From his observations on the tendency of alkali metal chelates to be solvated in polar media[24], Brandstrom proposed that the halogen atom of the reagent could co-ordinate to the metal, establishing an electronic link with the chelate ring π electrons. The transition complex (XII) would then form, and result in C- substitution. The possibility of an analogous intermediate (XIII) for the O- compound was rejected as being sterically unlikely. This mechanism was



XII



XIII

proposed for non-polar media, where the reagent would have little competition from the solvent in co-ordination to the metal. Polar solvents could be expected to prevent this attack by the reagent, and experimentally it was found that under such conditions the nature of the metal exerted little control over the reaction[48]. However, the mechanism could not explain the observation that C- substitution increased in polar solvents and decreased under less polar conditions.

The conception of a co-ordination mechansim has been strenthened by the inability of some copper and nickel chelates to react in the presence of pyridine, which strongly solvates the metal ions[48]. Also, some copper chelates have yielded, as reaction intermediates, chloro- copper (II) chelates[49,50] of both the parent diketone and of its C- substituted derivative. This arises from the difficulty of increasing the copper co-ordination number above five, which prevents co-ordination of more than one reagent molecule at a time, thus causing a two-stage reaction.

Nesmeyanov[46] has qualitatively explained the experimental observations on the basis of the metal-ligand bonding and the electrophilicity of the reacting halide. Where the charge on the metal ion has been neutralised by the ligand, i.e. in highly covalent systems, the central carbon atom will have a high degree of negative charge; thus, S_N1 reagents will favour C- substitution, but S_N2 halides will give mainly O- compound. Where the chelate is more ionic, the opposite trend is expected.

A comprehensive study of the acylation reaction has been made by Murdoch and Nonhebel[48], who concluded that chelates of metals capable of further co-ordination (copper, nickel, sodium and barium) reacted by Brandstrom's co-ordination mechanism. However, they also believed that the O- compounds were formed similarly i.e. that the intermediate (XIII) could exist. Where no co-ordination to the metal was possible (zinc and mercury), a concerted 'four-centre' reaction was envisaged, causing the breakage of the metal-oxygen bond, with the invariable production of a high proportion of O- compound.

Where the co-ordination mechanism occurred, it was found that S_N1 halides gave more ester than did reagents of S_N2 character, in agreement with Nesmeyanov's predictions. Further, S_N2 reagents reacted more rapidly than S_N1 compounds, which also suggests a co-ordination rather than a carbonium ion mechanism.

The end-groups of the ligandexerted a marked control over the direction of reaction. Bulky groups such as t-butyl or isopropyl increased the yield of triketone (C- compound), since the intermediate (XIII) was sterically hindered. Conversely, electron-attracting groups gave more O- compound; this was due to the reduced covalency and charge delocalisation within the chelate ring, preventing the central carbon atom from attaining a negative charge; and also to the reduced neutralisation of the charge on the metal ion, which inductively increased the carbonium ion character of the reaction, and thereby favoured O- acylation.

Increased polarity in the reaction medium was found to improve the yield of C- compound. This was rationalised in two ways, firstly because such polarity would facilitate charge delocalisation within the chelate, thereby increasing the charge on carbon; and, secondly, it was considered that transient solvates of the complexes were formed, with structures suitable for the formation of the intermediate (XII). This latter proposal was based on an observed increase in reaction rate in polar solvents.

The effect of the metal was not clear, with the exception of the two broad mechanisms mentioned. It appears that the important factor is the degree of ionisation of the metal-ligand bonding, which depends on the metal and diketone as already observed.

CHAPTER 2

ENOLISATION OF β-DIKETONES

Extent of Enolisation

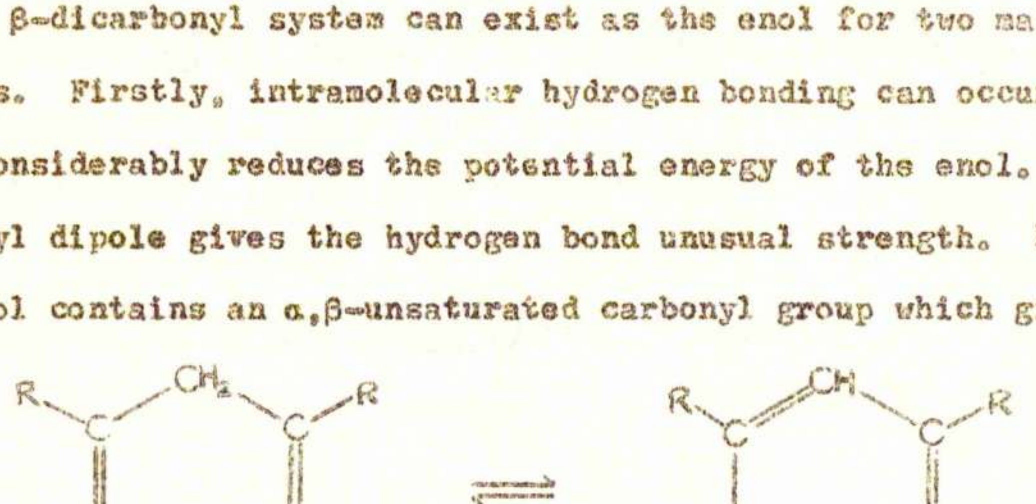
Keto- enol tautomerism (XIV) occurs widely in organic chemistry. The position of equilibrium between the tautomers is determined by

$$-CO.CH_2- \rightleftharpoons -\underset{\displaystyle OH}{C}=CH-$$

XIV

the relative stabilities of the structures, and can therefore vary widely. Simple carbonyl compounds exist almost exclusively in the keto form, since the potential energy of this system, obtained by the summation of individual bond energies[18,51], is less than that of the enolic isomer. Small amounts of enol may be detected[52], and these account for many reactions of the carbonyl group, such as the series of condensation reactions.

A β-dicarbonyl system can exist as the enol for two main reasons. Firstly, intramolecular hydrogen bonding can occur, and this considerably reduces the potential energy of the enol. The carbonyl dipole gives the hydrogen bond unusual strength. Further, the enol contains an α,β-unsaturated carbonyl group which gives

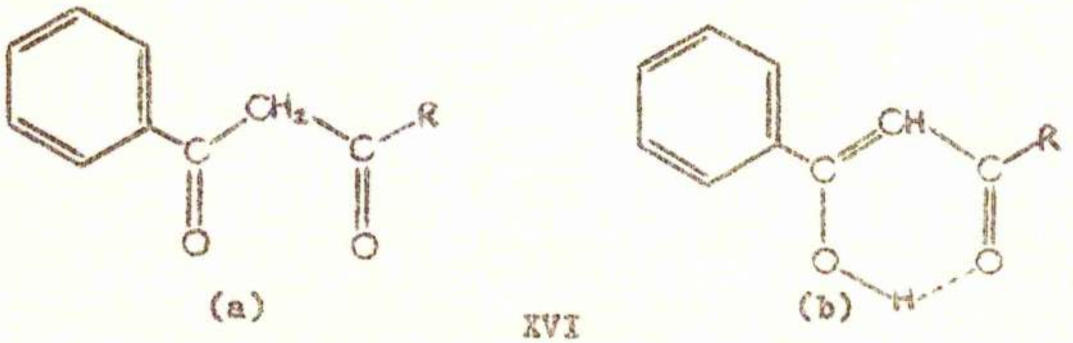


XV

resonance stabilisation to the system. The combined reductions in potential energy make the enol more stable than the diketo form, e.g. acetylacetone exists as 76% enol.

The hydrogen bonded 'chelate' structure of the enol, suggested by Sidgwick[53], has been confirmed by spectroscopic data[16] and is reflected in the physical properties of diketones. Thus the enol of ethyl acetoacetate is more volatile than the keto-isomer, in contrast to simple aldehydes and ketones whose enols tend to undergo intermolecular association, with a resultant loss in volatility. The strength of the hydrogen bond is further evident in the reluctance of many diaroylmethanes to undergo esterification, Schiff-base formation or reaction with diazomethane. There is an apparently high electron delocalisation within the enol ring.

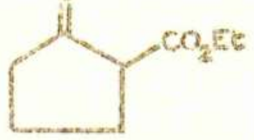
When the enolic resonance can extend to other unsaturated systems without the ring, the equilibrium tends to favour the enol even more. This is particularly evident in the presence of one or more phenyl groups. Thus ethyl benzoylacetate contains 21% enol as compared to 8% in ethyl acetoacetate. Similarly acetylacetone is enolised to the extent of 76%, benzoylacetone has 89% and dibenzoylmethane is completely enolic[54]. This enol stability arises from the cinnamoyl resonance in (XVIb). Other series which



(a) (b)

XVI

show this resonance effect are the cyclopentanone and cyclohexanone compounds shown (XVII - XXI)[55,56,57].

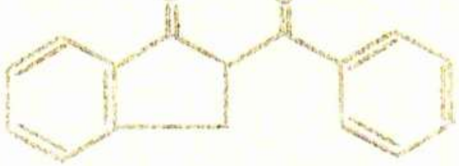


5% enol

XVII

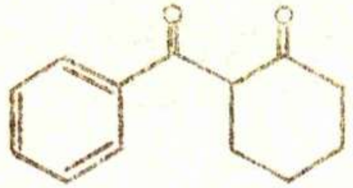
25% enol

XVIII



78% enol

XIX



3% enol

XX

25% enol

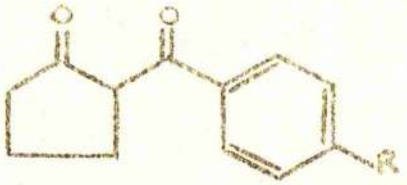
XXI

Where resonance occurs at the expense of the enol system, the equilibrium shifts to favour the keto form. This occurs in β-ketoesters (XXII), where the resonance interaction between the

XXII

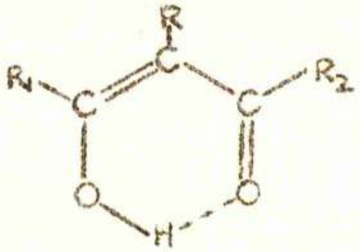
alkoxy and carbonyl groups interferes with the enol resonance[16]. Thus, diethyl malonate contains negligible enol[52,58], ethyl acetoacetate contains 8%, while acetylacetone is 76% enolic.

The inductive nature of substituent groups in the diketone has an effect on the tautomer equilibrium. The greater the electron affinity of the end groups (R in XV), the greater the proportion of enol; thus a typical series is $R = CO_2Et > C_6H_5 > CH_3$ in extent of enolisation. Similarly trifluoroacetoacetic ester contains more enol (89%) than acetoacetic ester (80%)[38], due to the higher electronegativity of the fluorine atoms. The extent of enolisation produced by various substituents in para-substituted-2-benzoylcyclopentanones (XXIII) shows a similar trend[33]: $NO_2 > Br > I > H > CH_3 > CH_3O$.



XXIII

This inductive effect is also shown by diketones substituted in the central carbon atom (XXIV). Increasing electronegativity

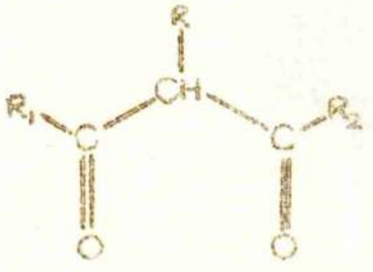


XXIV

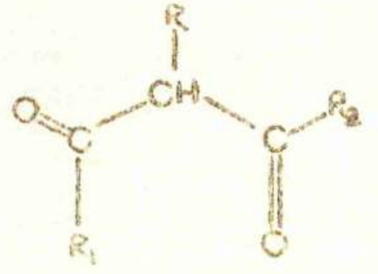
in this substituent R gives a corresponding increase in enol content. Thus in substituted acetoacetic esters (XXIV, $R_1 = CH_3$, $R_2 = OEt$) the enol content follows the order $R = CO_2Et > C_6H_5 > H > CH_3 > C_2H_5$[16].

The probable rationalisation of the inductive effect is that highly electronegative substituents facilitate the ionisation of the α-hydrogen atom in the diketo form, aiding the formation of the enol.

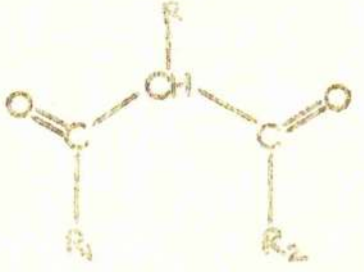
Three main conformations of β-diketones are (XXV - XXVII).



XXV



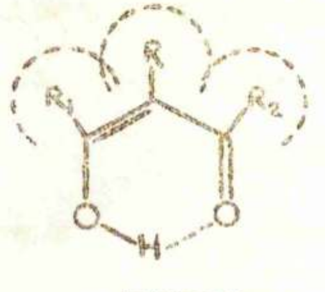
XXVI



XXVII

When the groups R_1, R and R_2 are large, steric interaction will result, and all forms will be strained. Since the form (XXV) is destabilised by the dipole-dipole interaction of the carbonyl groups, (XXVI) and(XXVII) probably better represent the diketone conformations. It can be seen that when R_1 and R_2 are large, steric interaction with each other, or with the central substituent R, will result, and consequently destabilise the keto form. This is experimentally verified in the series $RCOCH_2COR$, where the enol content is found to decrease in the order R = $Bu^t > Pr^i > CH_3$[60], i.e. large end groups increase the extent of enolisation.

Consideration of the enol structure (XXVIII) shows that when



XXVIII

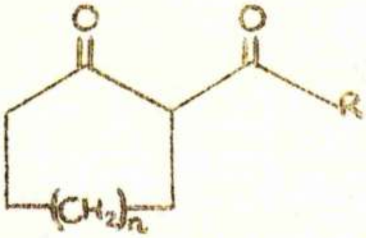
the cental substituent R is large, it will interact with the end groups R_1 and R_2, thereby destabilising the cis- chelated enol[61].

This is clearly substantiated by the following series:

$R_2 = Ch_3$ $R_3 = CO_2Et$	R=	H	CH_3	C_2H_5	$CH(CH_3)_2$[61]	(gas phase)
	% enol=	48	14	10	6	
$R_1 = R_3 = CH_3$	R=	H	CH_3	C_2H_5	$CH(CH_3)_2$[61]	(liquid phase)
	% enol	76	30	26	0	

Recent unpublished work has confirmed Hammond's observation[60] that the liquid dipivaloylmethane ($R = H$, $R_1 = R_3 = Bu^t$) is completely enolic, whereas its C- benzoylated derivative exists exclusively as the triketone[62]. Where R is large, the unusual existence of trans-enol has observed[61].

A less general steric factor arises in diketones in which one carbonyl group is contained in a ring system (XXIX). The enol content of such compounds is found to alternate with consecutive



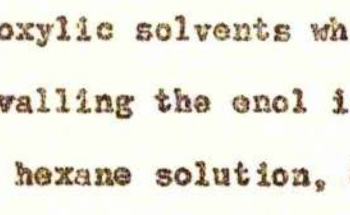
XXIX

rings, i.e. where one compound has a high enol content[63], the next homolog has a relatively low proportion, the next gives a high value and so on. No satisfactory explanation of these observations has been devised[63]. Since a coplanar enolic ring is required for true resonance stabilisation, it may be that the bond angles of the homologous series alternately favour and inhibit such planarity. A further point concerns the position of the enolic double bond in such a system; Brown[64,65] empirically proposed that cyclopentanone ring systems favoured exocyclic double bonds as a result of the carbon-carbon bond angles, and similarly that cyclohexanones favoured the endocyclic form. Thus in cyclic keto-esters (XXIX, R = OEt) where only the ring carbonyl group may enolise, consecutive members may be alternately hindered and favoured by the enolic double bond. This is not wholly satisfactory, since a similar, though less pronounced, periodicity is observed in 2-aldehydocyclanones (XXIX, R = H)[83,86].

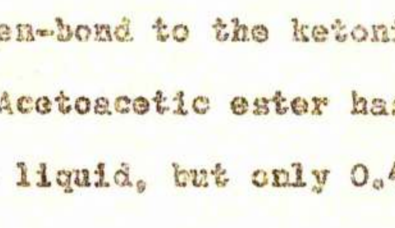
For any given compound, the position of the equilibrium is dependent on the surrounding media. Thus, the enol content may vary between the gas phase, the liquid phase, the solid phase and solutions. In solution, the polarity of the solvent has a marked effect, since the more polar keto-isomer is favoured by polar media, and especially by hydroxylic solvents which may hydrogen-bond to the ketonic isomer, thus rivalling the enol in stability. Acetoacetic ester has 46% enol in hexane solution, 8% as the pure liquid, but only 0.4% in water.

Direction of Enolisation

Unsymmetrical diketones can in theory produce two distinct isomeric enol structures (XXX and XXXI). The problem arises as



XXX

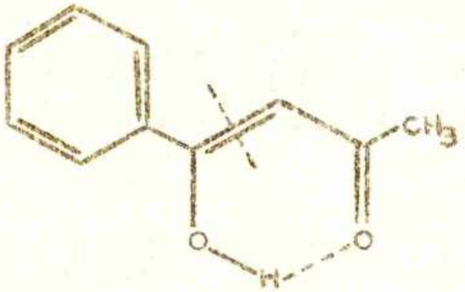


XXXI

to whether these isomers are truly distinct, particularly where a strong hydrogen bond exists, and if so whether one is preferred to the exclusion of the other.

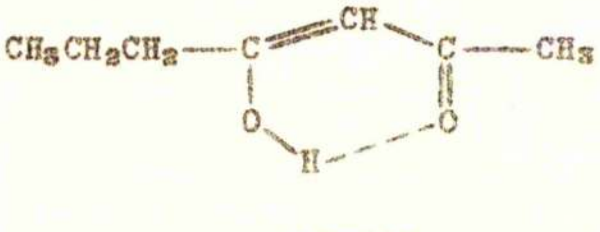
Most early investigations of the direction of enolisation utilised chemical methods, both degradative and synthetic. Physical techniques, in particular spectroscopic analysis, have been employed in more recent years. These methods are best described by particular examples which show the relative advantages and problems associated with any given procedure.

Controlled oxidation of an enol could be expected to cleave the double bond, thus yielding two fragments whose structure would indicate that of the enol. Ozone has been used in several instances as a selective oxidising agent for this purpose. Benzoylacetone[67] was degraded in this way to benzoic acid and methyl glyoxal, establishing the structure as XXXII, in agreement with the cinnamoyl resonance which would be expected.

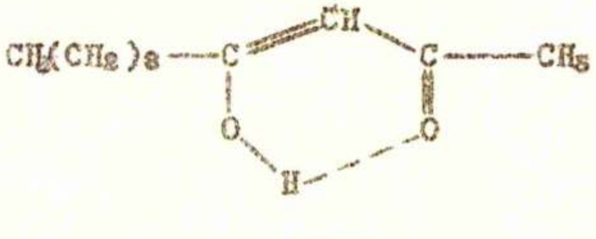


XXXII

Similarly acetyl-n-butyrylmethane (XXXIII) and acetyldecoylmethane (XXXIV) were found to have the enol structures shown[68].



XXXIII.



XXXIV.

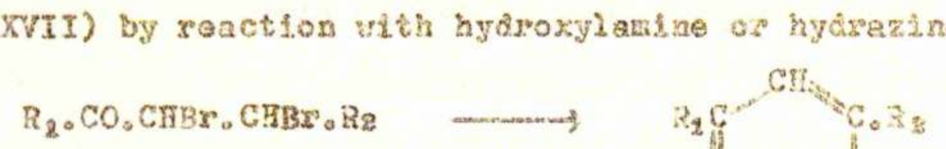
A more generally used technique has been to prepare a derivative of the diketone, utilising the reactivity of one oxygen atom, and to establish the structure of this compound, which may often be related to the enol structure.

Examples of the derivatives commonly used are isoxazoles (XXXV) obtained by reaction with hydroxylamine, and pyrazoles (XXXVI) which are obtained from hydrazine[69,70,71].

XXXV

XXXVI

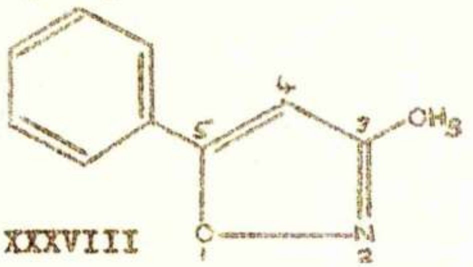
Two possible isomeric isoxazoles occur, and with substituted hydrazine, two pyrazoles are possible. The isomeric pairs can be synthesised unequivocally[72] from the appropriate α,β-dibromoketone (XXXVII) by reaction with hydroxylamine or hydrazine in alkali.



$R_1.CO.CHBr.CHBr.R_2 \longrightarrow$

XXXVII

It is therefore possible to assign a structure to the compound or mixture of compounds obtained from the diketone. Since hydroxylamine and hydrazine are typical carbonyl reagents, it would be expected that these derivatives are formed by attack on the carbonyl group of the enol, followed by elimination of water. This is substantiated by the fact that benzoyl acetone (XXXII) yields exclusively 3-methyl-5-phenylisoxazole (XXXVIII), showing that



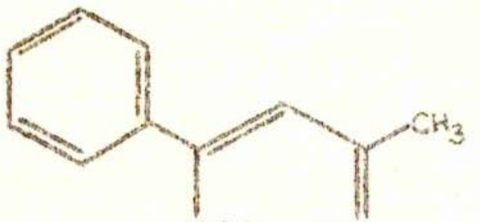
XXXVIII

the reagent has attacked the carbonyl group of the parent enol. This mechanism has been further confirmed by the occasional isolation of the intermediate oximes and hydrazones[74,75,76], which readily cyclise to yield the isoxazole or pyrazole.

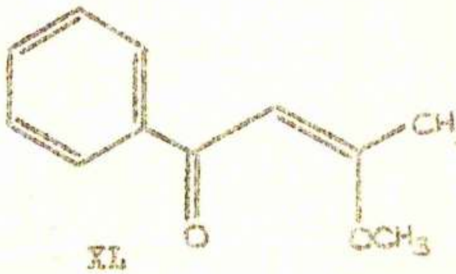
Weygand[77] found evidence that the enol ethers of some diketones reacted with hydroxylamine by a 1,4-addition to the enone system, followed by elimination of water. Barnes and co-workers, in a series of papers concerning the isoxazoles of diaroylmethanes[74,78-86], were inconsistent in their interpretation of the mechansism by which the diketones reacted, sometimes assuming attack on the carbonyl group and sometimes on the 1,4-conjugated system. However, Blatt[87] demonstrated that hydroxylamine invariably attacked the carbonyl group of α,β-dibromoketones, α,β-unsaturated ketones and α-bromo-α,β-unsaturated ketones, thus ruling out the 1,4-mechanism.

Barnes, and earlier, Wheeler[78], in studies of the isoxazoles, were unable to detect a regular behaviour pattern in relation to the diketones. The occasional isolation of isoxazole mixtures[82,86] suggested a mixture of the enolic modifications, but this is not in agreement with physical data, which indicate the presence of a single compound.

Enol ethers and esters are readily formed by many diketones, by normal procedures. Acetylacetone gives the O-methyl ether with diazomethane[18], as do many other diketones, and enol-esters may be formed by reaction with an acid chloride[48] or anhydride. Weygand[89] found that with diazomethane or dimethyl sulphate, benzoylacetone gave one methyl ether (XXXIX), whose structure was proved by



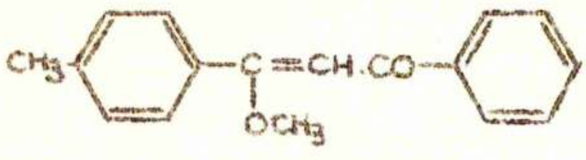
XXXIX



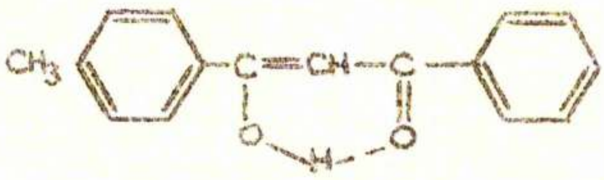
XL

synthesis, and by ozonolysis to yield methyl benzoate. Thus the enolic carbonyl is apparently attacked. Eistert and Merkel[70] obtained an ether from benzoylacetone and diazomethane, but assigned the isomeric structure (XL). They point out that this does not necessarily prove the enolic structure, since the rate of interchange of the tautomers may well be greater than the reaction rate.

Weygand[77] later found that diazomethane and p-methyldibenzoylmethane gave the ether(XLI), and by analogy with his benzoylacetone



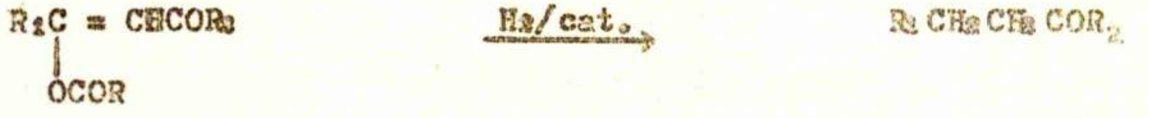
XLI



XLII

work, this indicated that the enol is(XLII). This structure is reasonable, since the carbonyl-oxygen atom nearer the tolyl ring should, by induction, be the more negative and would therefore be expected to attract the enolic proton. An analogous result was found for p-methoxydibenzoylmethane, and so the cumulative evidence suggests that diazomethane attacks the enolic centre.

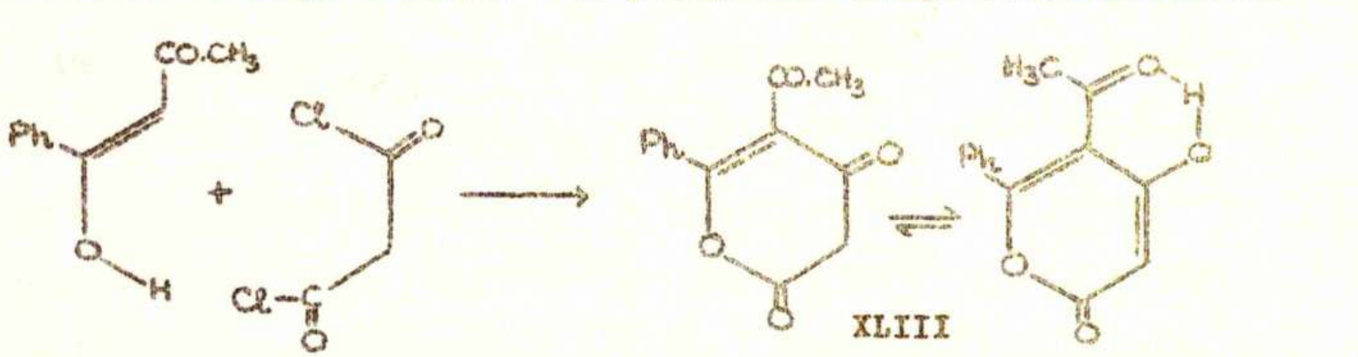
The structures of enol esters have been shown by hydrogenolysis to the corresponding saturated ketone[91]. Only one isomeric



$$R_1C(OCOR) = CHCOR_2 \xrightarrow{H_2/cat.} R_1CH_2CH_2COR_2$$

ester has been isolated from any given diketone, although geometrical isomerism occasionally arises[91]. The same compound is obtained from the diketone and from its metal complexes[48,91,92]. In the cases of benzoylacetone[69], benzoylisobutyrylmethane[48] and benzoyl-n-butyrylmethane[48], attack has invariably been shown to occur at the carbonyl group in the enol structure.

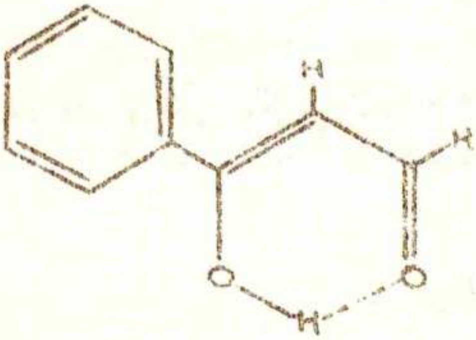
Malonyl chloride reacts with β-diketones to form hydroxypyrones[93], by attacking the double bond and hydroxyl group, as shown for benzoyl acetone. The phenyl and acetyl substituents in



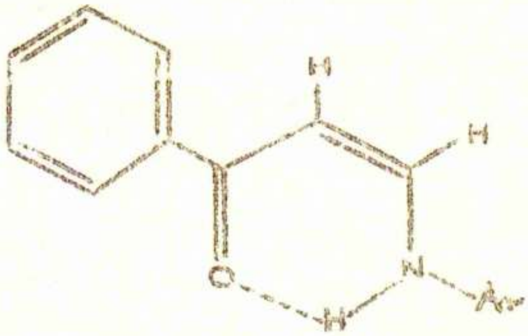
XLIII

the product (XLIII) show the direction of enolisation; the alternative enol would yield benzoyl and methyl substituents. The alternative product structures may be differentiated by spectroscopy.

Spectroscopy is frequently useful in assigning a structure to an enol. The use of nuclear magnetic resonance is especially well exemplified in the case of benzoylacetaldehyde[58] XLIV. The spectrum of this compound showed the enolic proton as a singlet (by integration the compound was shown to be completely enolic), while the aldehydic proton appeared as a doublet, due to coupling

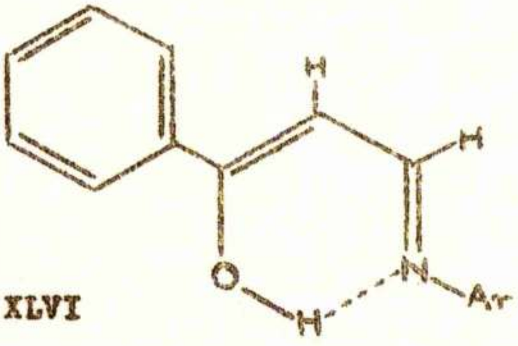


XLIV



XLV

with the adjacent vinylic proton. The failure of the enolic hydrogen to interact with the aldehydic proton shows the structure to be the expected one(XLIV). A variety of Schiff's bases were prepared, and these all showed a hydrogen-bonded proton as a doublet, due to interaction with the α-hydrogen (XLV). This signal disappeared on deuteration, and the 'aldehydic' signal reduced from a multiplet to a doublet. Thus, these compounds all had the structure (XLV). Apparently the stability of the amino group over the alternative imino-system (XLVI) is sufficient to overcome the usual styryl resonance effect.



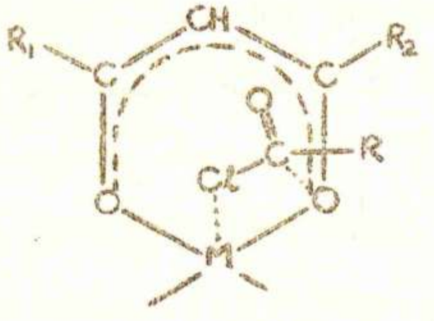
XLVI

Although the above example is unusually clear, analyses of infrared, ultraviolet and nuclear magnetic spectra have given results in other cases.[54]

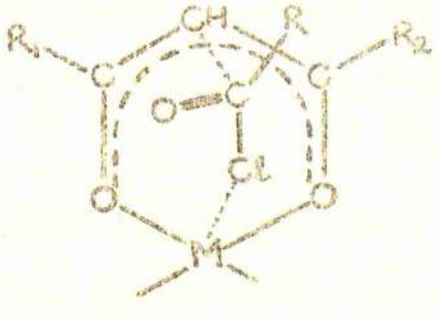
CHAPTER 3

THE ACYLATION OF THE METAL CHELATES

Mention has already been made of recent work[48] on the factors which control the position of acylation of metal chelates. It was concluded that as the electron-affinity of the ligand end-groups increased, so the reactions yielded a greater proportion of ester ('O- compound'). In accordance with the theory of Nesmeyanov[49], this effect was attributed to the increasing positive charge on the metal in the chelate ring, resulting in a greater degree of carbonium ion character in the acylating agent on formation of the co-ordination intermediates I and II. Thus, attack on the more electronegative centre, i.e. the oxygen atom, will increase.



I



II

These conclusions were based on the reactions of benzoyl chloride with the metal chelates of diisobutyrylmethane (DiBM), benzoylisobutyrylmethane (BiBM), benzoyl-n-butyrylmethane (BnBM) and di-n-butyrylmethane (DnBM), all in cyclohexane solution. The results are summarised in the following table.

Percentage C- acylation in Reactions of Metal Chelates with Benzoyl Chloride.

Metal	DiBM	BiBM	BnBM	DnBM
Copper	99.0	47.5	30.5	34.5
Nickel	83.5	43.0	44.5	35.5
Sodium	79.5	68.0	39.5	42.0
Barium	86.0	42.0	32.5	35.5

Comparison of the BiBM chelates with the corresponding DiBM series shows a marked decrease in C- acylation, which was attributed to the electron-attracting inductive effect of the phenyl group in the former compounds.

A similar effect would be expected between the DnBM and BnBM series, and, with the exception of the nickel chelates, this is experimentally verified. However, the difference between these series is much smaller, and in fact is of the same order of magnitude as the maximum experimental error observed in tests.

Although the steric hindrance to O- acylation in either of the above pairs is apparently constant (since attack always occurs at the carbonyl-oxygen atom adjacent to the alkyl group), the greater differences observed in the branch-chain series may in part be due to the steric inhibition by the bulkier isopropyl end-group.

Chelates of BiBM give more C- compound than do those of BnBM, with the exception of the nickel complexes, and although this would be expected by virtue of the greater electron-affinity of the n-propyl group, it may also be due to the steric hindrance to O- attack in the isobutyl series.

Thus, the experimentally observed figures cannot with certainty be attributed exclusively to the different electronic characters of the ligands.

The aim of this research was to extend these investigations to systems more suited to changes in electronic character without corresponding steric variations.

Dibenzoylmethane was chosen as the basic diketone system for this purpose, since it was likely that introduction of a series of different functional groups into the para-positions would change the electronic nature of the chelate, without causing any changes in the steric environment of the neighbouring carbonyl-oxygen centre.

To facilitate comparison of the results with the earlier work, the same metals and conditions were used as far as was practicable.

The chelates of p-nitrodibenzoylmethane and p-methoxydibenzoylmethane with copper, nickel, sodium, barium and zinc were prepared and purified. In comparison to the alkyl series, these compounds were found to be highly insoluble, and it was necessary to carry out the reactions in benzene solution rather than in cyclohexane. The work on dibenzoylmethane chelates was therefore repeated in this new solvent.

After preliminary reactions, the methoxy-series was found to give inconclusive results, and so the work was further extended to chelates of p-methyldibenzoylmethane (copper, nickel and sodium).

The ultraviolet spectra of the chelates are very similar to those of the corresponding diketones. Only the p-methyl compounds show a distinct bathochromic shift in the absorption wavelengths. Thus the bonding in these complexes is primarily ionic in nature, with the p-methyl series having the greatest degree of covalency. This observation is in agreement with the findings of Fernelius[94], who showed that chelate stability decreased as the acidity of the parent ligand increased. The more covalent the bonding, the more stable the chelate, and so the ionic nature of these compounds is indicative of relative instability. Also, the electron-affinity of the series is $NO_2 > H > CH_3$, and so the acid strengths of the corresponding diketones will be in the same order. It is of interest that the methoxyl group, normally considered as more electron-repellant than methyl, does not induce the expected covalency in the chelates.

Carbonyl absorption in the infrared shows that the complexes contain no 'free' carbonyl groups, but typical 'chelate carbonyl' frequencies are present. Thus the compounds are true chelates, with both oxygen atoms bonded to the metal, despite the ionic nature of the linkage.

In the reactions of the chelates, the triketone products were isolated by alkali extraction. The nitro-chelates also yielded an enol-benzoate of the triketone, which was separately isolated by fractional crystallisation. This was assumed to be formed by secondary reaction of p-nitrotribenzoylmethane with benzoyl chloride, and the total C- compound was calculated from the sum of the ester and triketone yields.

The results of the reactions are summarised below as the average percentage of C- compound obtained in at least two experiments consistent to a maximum error of 5%.

Average Percentage C- benzoylation of Substituted Dibenzoylmethane Chelates (2% in Benzene).

Substit.	Copper	Nickel	Sodium	Barium	Zinc
p-NO_2	*20.2	*2.5	*20.6	*35.4	11.1
p-H	*23.4	*36.1	*33.4	*29.6	8.6
p-CH_3O	*22.1	41.0	*29.1	-	12.8
p-CH_3	*60.1	63.1	*57.8	-	-

(* = heterogeneous reaction mixture.)

From these results it is clear that the expected trend of C-acylation, i.e. $NO_2 < H < CH_3 < CH_3O$, is not followed in practice. It can be seen that the methyl series invariably gives the greatest yield of triketone, and the nitro-chelates the least (with the exception of the barium complex).

Not only does the methoxy-series invariably give less C- compound than the methyl, but the copper and sodium chelates of this group give less C- acylation than the corresponding complexes of dibenzoylmethane itself.

The methoxyl group generally behaves as an electron-repellant entity in the mesomeric effect, and to a much greater extent than does the methyl function. However, it appears thatthe less common inductive effect of the group, which acts in the opposite sense, also exerts control in the chelate system, with the net result being a virtual 'cancellation' of electron control. Thus the methoxy-chelates give yields of triketone similar to those from the unsubstituted complexes. This conclusion is further supported by the lessor degree of covalent bonding in the methoxy-compounds than in the methyl analogues, as shown by their ultraviolet absorption spectra.

Although no simple picture of the effect of the metal may be seen in these results, several points are worthy of note in this respect.

The zinc chelates give a low yield of triketone, reasonably independent of the substituent, in support of the proposed separate mechanism of reaction of these compounds[48].

Of the remaining metals, only nickel shows a regular trend of product ratio in relation to the electronic character of the ligand-substituent. However, the metals (copper, nickel, sodium and barium) whose chelates react through the co-ordination mechanism, give products of broadly similar composition for any given ligand. The range of metals and diketones is too limited to accept this statement without considerable extension of the work.

Several problems became evident during these experiments, and these limit the usefulness of the results in any analysis of the acylation reaction.

As already mentioned, all the chelates are more ionic in nature than those used in the initial experiments, and consequently the yields of triketones are much lower. Only the methyl-series gives more than 40% of C- compound. Since this latter compound was the one isolated from the reactions and used to find the product ratio, any experimental error is of greater significance than before; for example, the methoxy- and hydrogen-series are always within 5% of each other and thus are not strictly differentiable within the experimental error. Thus, the only strictly valid comparisons are those between the methyl series and any other.

A second problem is caused by the generally high insolubility of the chelates, due in part to their ionic structures, and also to the aromatic nature of the ligands. Many of the reaction mixtures, particularly those of the nitro-compounds, were initially heterogeneous. Kornblum[95] has shown that phenoxides give C- substitution on heterogeneous reaction, and by analogy the chelates should do likewise. This is confirmed by a comparison of the yields of tribenzoylmethane obtained from the chelates of dibenzoylmethane in cyclohexane[48] with the present work using benzene. The latter solvent, with greater power of solution, gives markedly less triketone than do the cyclohexane reactions, with the exception of the nickel chelate (the most soluble of the co-ordinating complexes). Thus many of the figures obtained reflect this heterogeneity factor along with the electronic nature of the ligand. Copper and sodium give highly insoluble products, barium gives distinctly more soluble chelates, and the nickel and zinc complexes are the most soluble of all.

As already mentioned, p-nitrotribenzoylmethane itself gives an enol-benzoate, and so the figures quoted combine both this ester and the free triketone yields. Although the ester is probably formed by secondary reaction of the triketone, the possibility of its primary formation from the chelate, with an accompanying effect on the product ratio, cannot be excluded.

Copper p-nitrodibenzoylmethide gives an intermediate complex which, by analysis and reactions, was shown to be chloro-copper (II)-p-nitrodibenzoylmethide. Such complexes have already been mentioned, and arise from the inability of cupric chelates to co-ordinate more than one molecule of acyl halide at a time. Thus, the first stage of the copper reactions differs from the second, where the reagent co-ordinates to a separate system, and so the reactions of the copper chelates cannot be validly compared with those of complexes which can co-ordinate two molecules of reagent.

The structures of the enol-esters obtained from the reactions show that O- acylation occurs at the carbonyl group adjacent to the phenyl group in the methyl- and methoxy-compounds, but at the oxygen near the substituted ring in the nitro-system. The question therefore arises as to whether the substituent controls only the adjacent metal-oxygen bond, or whether the electronic effect extends over the whole dicarbonyl system. Only if the latter alternative holds true can the systems be compared.

Whereas the substituted chelates give only one ester and so have only one oxygen atom available for attack, two oxygen-centres are available in the dibenzoylmethane complexes. Statistically, this latter series should therefore yield an 'artificially' low percentage of triketone in comparison to the other compounds.

For a true representation of the electronic effect, it was necessary to eliminate or minimise these issues as far as possible.

The solubility problem is solved by considering only the nickel and zinc chelates, which are the most soluble. Since zinc chelates do not react by the co-ordination mechanism, a study of nickel chelates is indicated. These compounds are especially suitable because of their relative solubility, rapid rates of reaction and because of the ready interchange of the nickel co-ordination number between 4 and 6. It is significant that the nickel chelates already examined show the expected trend.

The nickel chelates of p-chloro-, p-bromo-, m-bromo- and p-methyl-p'-methoxydibenzoylmethane were accordingly prepared and their reactions examined. The complete series of nickel reactions is tabulated below.

Average Percentage C- benzoylation of Nickel Chelates of substituted Dibenzoylmethanes (2% in Benzene).

p-NO$_2$	m-Br	p-Br	p-Cl	p+H	p-CH$_3$O	p-CH$_3$O p'-CH$_3$	p-CH$_3$
*2.5	22.6	26.0	29.4	*36.1	41.0	*47.2	63.1

(* = heterogeneous reaction mixture.)

Taking the dibenzoylmethane chelate as a zero-point, it is at once apparent that electron-withdrawing groups (nitro and halogen) lower the yield of C- compound, whereas electron-repelling functions (methyl and methoxyl) increase this product. This is in agreement with the trend expected on the basis of the co-ordinati mechanism.

A more refined picture can be obtained by comparing the relative effects of each substituent with the effect produced on the product ratio. The observation that the methoxyl group exerts both its inductive and mesomeric effects is further borne out by the fact that nickel p-methyl-p'-methoxydibenzoylmethane gives a yield of triketone intermediate between those obtained from the p-methyl and the p-methoxy analogues.

Further, although the chlorine atom is more electronegative than bromine, the p-bromo-chelate gives the lesser C- acylation of the two. This is in agreement with the existence of a balance between the inductive (+I) and mesomeric (-M) effects of the halogen atom. Introduction of a bromine atom into the meta-position, where the inductive effect has increased power, gives a further reduction in C- acylation.

Thus the yield of C- compound increases in proportion to the electron-repelling power of the ligand end-groups.

O-acylation occurs at the oxygen atom next to the substituted ring in the p-nitro-, m-bromo- and p-methyl-p'-methoxy-compounds (in the latter, adjacent to the tolyl ring), but in every other case next to the phenyl group. Since these changes do not disturb the trend of the product ratio, it must be concluded that the substituent groups influence a delocalised electron-system within the chelate ring, and not simply the adjacent metal-oxygen bond.

The conclusions drawn from this work can be summarised as follows.

Dibenzoylmethanes give true cyclic chelates with the metals studied, but the metal-ligand bonding is primarily ionic. These chelates contain a delocalised electron system within the chelate ring, and this is distinctly affected by the electronic nature of the ligand end-groups. Where these end-groups have opposing inductive and mesomeric tendencies, the two balance out to give a net result in the same sense as the stronger of the two effects.

With the exception of the zinc complexes, the chelates react with benzoyl chloride to give the corresponding tribenzoylmethanes in yields which increase in proportion to the electron-repulsion of the end-groups.

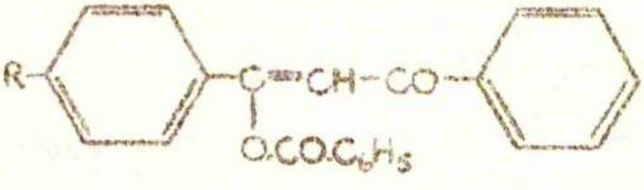
Copper, nickel, sodium and barium complexes are acylated by the co-ordination mechanism proposed by Murdoch and Nonhebel, whereas zinc chelates are forced, through lack of co-ordination ability, to react by some other process, either ionic or a concerted four-centre process.

CHAPTER 4

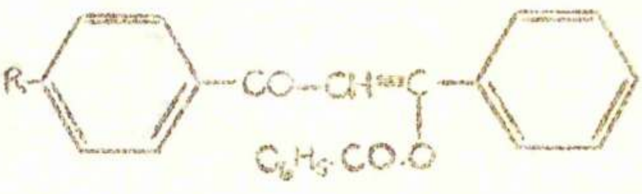
ENOLISATION AND REACTIONS OF THE DIKETONES

Asymmetrical β-diketones can in theory give two isomeric enol esters, and so the problem arises as to whether one isomer will be preferred to the other, and if so, what factors will determine the preferred structure.

This question arose in the study of chelate reactions already described. In the initial experiments using p-nitro- and p-methoxydibenzoylmethane, it was found that the ester from the nitro-compound had the structure I (R = NO_2), while the methoxy-diketone gave



I

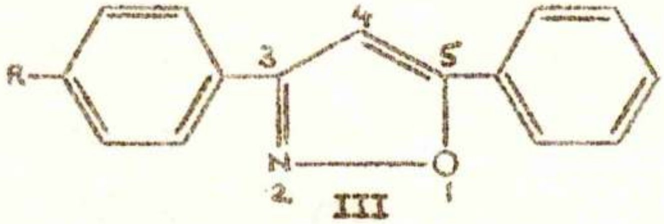


II

II (R = CH_3O). When the work was extended to include p-methyldibenzoylmethane, the ester II (R = CH_3) was obtained. Thus, the electron-attracting nitro group acted in the opposite direction to the methyl and methoxyl functions, as would be expected.

It was expected that the structure of the ester would be related to the enolic structure of the parent diketone. The absolute enol configurations of these compounds were in some doubt, owing to the uncertain mechanism of formation of the isoxazole derivatives, which have been mainly used in such studies of diaroylmethanes[72,74,90–95]. However, even without an absolute structure, it was seen that the nitro-diketone gave an isoxazole[96,97]

(III, R = NO_2) whose nitrogen atom was attached to the same carbon as was the ester group, whereas the methyl[72] and methoxy[80] isoxazoles



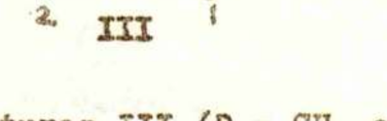
III

were said to have the structures III (R = CH_3 or CH_3O), with the nitrogen attached to the opposite carbon to that attached in the ester formation. This inconsistency made it desirable to establish configurations for the enols, and to relate these to the structures of the corresponding esters.

Comparing the above observations with the case of benzoylacetone, whose enol, enol acetate and isoxazole have already been shown to have the structures IV, V and VI, respectively, it can be seen


$\underset{\substack{|\\ \text{OH}}}{\text{Ph C}}=\text{CH.}\underset{\substack{\|\\ \text{O}}}{\text{C}}\text{.CH}_3$

IV


$\underset{\substack{\|\\ \text{O}}}{\text{Ph C}}-\text{CH}=\underset{\substack{|\\ \text{OCOCH}_3}}{\text{C.CH}_3}$

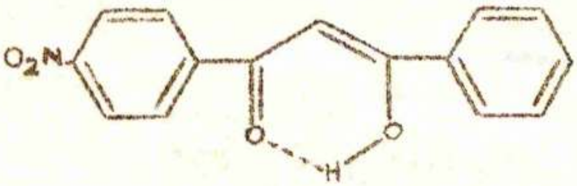
V


$\underset{\substack{|\\ \text{O}}}{\text{Ph C}}=\text{CH}-\underset{\substack{\|\\ \text{N}}}{\text{C.CH}_3}$

VI

that only the nitro-compounds follow this pattern, i.e. in attacking the carbonyl group of the enol. In view of the unexpected behaviour of the chelates derived from p-methoxydibenzoylmethane, this compound might be expected to behave anomalously, but such was not the case with the methyl series.

The isoxazoles of the three compounds were therefore prepared and re-examined. While the identity of the nitro-derivative was confirmed, it was found that the methyl compound had in fact the opposite structure (3-phenyl-5-tolyl-) to that given by Wheeler^{72}. Further, the product from p-methoxydibenzoylmethane was found to be a mixture of the two isomers, although the main component was that recorded by Barnes and Brandon^{80}. Thus, only the methoxyl group had anomalous behaviour, and by comparison with benzoylacetone, the other compounds should have the enolic structures VII and VIII.

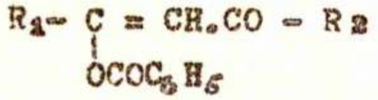


VII

VIII

When the chelate work was extended to other diketones, the structures of their enol benzoates were determined, and the identities of the derived isoxazoles established. Some of these isoxazoles had previously been assigned structures, but in view of the discrepancies already observed, it was decided to re-examine these cases with the aid of infrared and ultraviolet spectroscopy, which had not been available to the earlier workers. The isoxazole identities were found by independently synthesising the two possible isomers from α,β-dibromoketones. The evidence in favour of this being an unequivocal synthesis has been summarised by Wheeler^{72}. By melting point and mixed melting point data, and by comparison of the I.R., U.V. and, where solubility permitted, the N.M.R. spectra, the structures of the products obtained from the diketones were established.

The enol benzoates were hydrogenated over platinum to give benzoic acid and a ketone (IX) whose structure followed directly



$$R_1-\underset{\displaystyle OCOC_6H_5}{\underset{|}{C}} = CH.CO - R_2$$

$$R_1CH_2\,CH_2COR_2 + C_6H_5CO_2H$$

IX

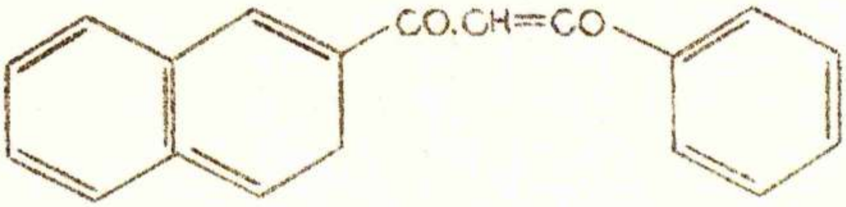
from that of the ester^{91}. This procedure, although workable, was not efficient, since the ketone was frequently hydrogenated further to the alcohol or even the hydrocarbon.

An attempt to synthesise the esters by reaction of silver benzoate with a monobromoketone was unsuccessful, even on prolonged reflux. The bromoketone was derived from the corresponding chalcone dibromide^{97}, and could have either of the structures X or XI. Earlier workers had considered the β-bromo form XI

$$R_1.CO.CBr = CH.R_2 \qquad\qquad R_1.CO.CH = CBr.R_2$$

X XI

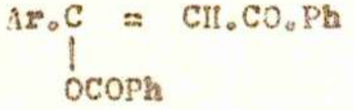
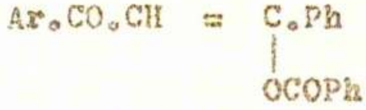
to be correct, and this was the basis of the attempted synthesis. The failure of the reaction was evidence of structure X, which was favoured by Barnes$^{78-86}$ and Blatt^{87}, and this was eventually proved correct, in the case of the β-naphthoylbenzoylmethane series, by comparison of the N.M.R. spectrum with that of the corresponding chalcone (XII).

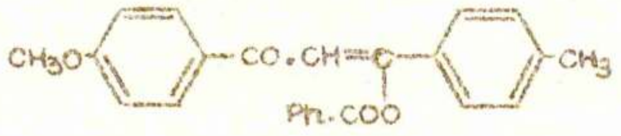


XIX

The structures assigned to the various derivatives are shown on the following page. This work was also extended to include some condensed aryl (α- and β- naphthyl) and heterocyclic systems.

Structures of Diaroylmethane -O- Benzoates.

 $\underset{\text{OCOPh}}{\text{Ar.C}} = \text{CH.CO.Ph}$	 $\text{Ar.CO.CH} = \underset{\text{OCOPh}}{\text{C.Ph}}$
Ar	Ar
p-nitrophenyl	p-methoxyphenyl
m-bromophenyl	p-methylphenyl
α-naphthyl	p-chlorophenyl
β-naphthyl	p-bromophenyl
Picolyl[98]	α-furyl



Structures of Isoxazoles from Diaroylmethanes.

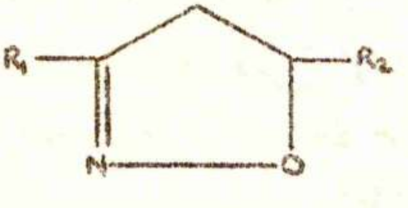
	
Ar	Ar
p-nitrophenyl	p-methylphenyl
*p-methoyxphenyl (86%)	*p-chlorophenyl (62%)
α-naphthyl	*p-bromophenyl (51%)
Picolyl	*m-bromophenyl (59%)
	*β-naphthyl
	*α-furyl


*

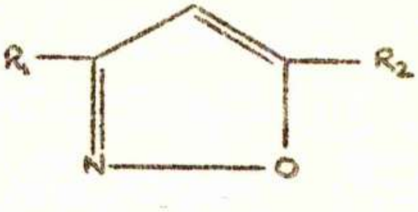
*Main product in mixture of isomers.

In every case, only one ester was isolated, whether by direct reaction of the diketone and benzoyl chloride in pyridine, or by benzoylation of a chelate in an organic solvent. Most of the diketones, however, gave a mixture of isomeric isoxazoles. The close physical and chemical similarity of these isoxazole pairs made separation impossible. Attempts to determine the proportions of the mixtures by means of Vierordt's method of ultraviolet analysis[99] were found to be insufficiently accurate. However, the figures obtained, which were in qualitative agreement with the deductions made from melting point data, with the exception of the p-methyl-p'-methoxy compounds, probably give a reflection of the trend, and are included in the table of results.

Having established the isoxazole identities, the problem of relating these to the enolic structure of the diketones was increased by the frequent occurrence of mixtures. Mention has already been made of the doubt concerning the mechanism of formation of the isoxazoles. Barnes[74,78-86] was inconsistent in his interpretation of this reaction, apparently because of the reaction of α,β-unsaturated ketones with hydroxylamine to produce oximes and



Isoxazoline.



Isoxazole.

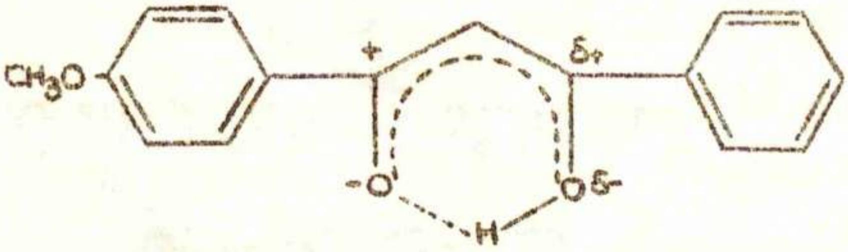
isoxazolines. Blatt[100] had reported that isoxazoline formation did not proceed via an oxime, and so Barnes assumed that a 1,4 mechanism occurred. Hence, on oxidation of the isoxazoline to the isoxazole , a product would be obtained with the oxygen atom attached to the carbon from the original carbonyl group. Barnes applied this deduction to the diketones themselves. Blatt later pointed out[87] that although the isoxazoline was not formed by simple attack on the carbonyl group, neither was it formed by a 1,4 addition, but by some other unspecified mechanism. He also clearly showed that the same isoxazole was formed from an α,β-unsaturated ketone and its corresponding α-bromo- and α,β-dibromo-compounds. In combination with the absolute evidence that benzoylacetone forms its isoxazole by attack on the carbonyl group, it becomes clear that where a single isomeric isoxazole is produced, it arises from attack on the carbonyl group of the parent diketone.

The isoxazole reactions were carried out in aqueous alcoholic solutions, using hydroxylamine hydrochloride. Under these conditions the diketones, which are extremely weak acids, are essentially unionised. Repetition of the reactions in alkaline solution (for the nitro, methoxy and methyl series) gave exactly the same products, and the reaction time was considerably increased. In alkali, an equilibrium will exist between the enolate anion and the diketone, and so isoxazole formation must involve the intact molecule, and not the anion. Under normal conditions, the diketones are completely enolic, and behave physically as single compounds. The N.M.R.

spectra show the enolic proton at negative τ values, and this signal disappears instantaneously on mixing the compound with heavy water, showing a highly ionic bond structure. However, the vinylic proton shows very little decrease in absorption intensity even after several days in contact with the deuterium source; indeed, dibenzoylmethane shows no exchange at all. Thus, there is very little of the diketo-tautomer present in the system. Mixtures of isoxazoles cannot therefore be explained by attack on the dicarbonyl structure, and the reaction must occur between the true enol and hydroxylamine. This is borne out by the nitro and methyl isoxazoles, both by the formation of one isomer in each case, and also by the structures of the products, which are formed by attack on the carbonyl which would have the smaller dipole in the corresponding diketo- form.

Barnes[84] has suggested that rapid interchange of the two possible enols occurs with one form reacting more rapidly than the other. Although this would explain the formation of mixtures, it is not in agreement with the behaviour of the nitro- and methyl-diketones, since the alternative enol would be the more reactive, in each case. Also, the N.M.R. spectra of benzoylacetaldehyde and its Schiffs bases clearly show a distinction between the preferred enol and its alternative isomer.

The evidence therefore suggests that attack takes place on one enolic structure, which has a charge distribution in the chelated ring, controlled by the substituents. Thus, when an electron-withdrawing group such as nitro is present, the adjacent carbonyl oxygen will, by induction, be the less negative of the two; consequently, the enolic proton will be attracted to the other oxygen atom, and the structure will be VII. Conversely, the electron-repellant methyl group will give the enol VIII. As with the metal chelates, the methoxyl group apparently balances its mesomeric (+M) and inductive (-I) effects, and both carbonyl-carbon atoms have a positive charge, with the greater proportion near the substituted ring (XIII). Thus the nucleophilic hydroxylamine molecule can attack both centres, resulting in a mixture of isoxazoles.



XIII

p-methoxy-p'-methyldibenzoylmethane also gave a mixture of isoxazoles, with the greater proportion being formed by attack on the anisoyl carbonyl group. However, there was a much greater proportion (probably about 40%) of the 3-tolyl-isoxazole in this case than there was of the 3-phenyl product with the simple methoxy-diketone. This result agrees with the opposing effect of the methyl and methoxyl groups in the disubstituted diketone, and confirms the conclusion concerning the delocalised system within the enol.

The halogenated diketones all gave isoxazole mixtures, with the 3-phenyl compound being the main component. Thus the benzoyl group has the greater carbonyl character in these systems, and the mesomeric effect (+M) of the halogen atoms counteracts the inductive effect (-I).

α-Naphthoylbenzoylmethane gave only the 3-(α-naphthyl) derivative, whereas the β-analogue gave a mixture whose main component was 3-phenyl-5-(β-naphthyl)-isoxazole. α-Naphthoic acid (pKa 3.7) is a much stronger acid than benzoic (pKa 4.20), and so the α-naphthyl group has a greater inductive effect than phenyl. Thus attack occurs exclusively on the naphthoyl carbonyl group. The β-naphthyl group (acid pKa 4.17) is more similar to phenyl, and this results in the mixture of products.

In the heterocyclic systems, the pyridine ring can only exert an inductive effect (-I), because the electron pair on nitrogen is tied up in the aromatic ring. Thus the 3-aryl isomer is the exlusive product. In contrast, the furyl ring has an electron pair on oxygen which can give the mesomeric (+M) effect along with the inductive effect (-I) of the oxygen atom, and this is reflected in the mixture of isoxazole products formed.

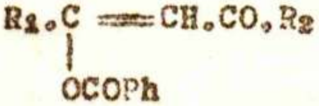
These results show that isoxazole formation is a reaction of the chelated enol, and demonstrate the presence of a delocalised electron system within the ring, controlled by the electronic tendencies of the diketone end groups. A close analogy is apparent in the properties of the metal chelates of the diketones. An interesting feature is that this system can provide an indication of the behaviour of aromatic systems, by a study of the isoxazoles produced by diketones containing these systems.

It appears that in diaryl diketones, the distinction between the enolic isomers is slight, since both have a similar resonance system. Where one substituent has a sharply distinct inductive or mesomeric character (e.g., nitro, methyl, α-naphthyl), the system behaves as a single enol, but in other cases, one carbon-oxygen bond acts as though it had only slightly more double bond character than the other. This is in agreement with the observations of Hammond[60], who found little interaction between substituents and the enol system; however, this probably results from a balancing of effects rather than from an absence of these.

Comparison of the structures of the enol benzoates with the isoxazoles immediately shows that esterification does not always occur at the oxygen of the 'carbonyl group' in the enol, as suggested by the benzoylacetone compounds. Although diketones which yield a single isoxazole (p-nitro, p-methyl, α-naphthyl) all esterify at the corresponding oxygen atom, those which give isoxazole mixtures may esterify at the position corresponding to the major component (p-chloro, p-bromo, α-furyl) or to the minor (p-methoxy, m-bromo, β-naphthyl).

Two factors suggest that esterification does not arise directly from the enol. Firstly, every diketone gave a single isomeric ester whether by direct reaction or from its chelates. This is in marked contrast to the isoxazole reactions, which have been shown to involve the enol as such. Secondly, the greater polarity of benzoyl chloride, as compared to hydroxylamine, would be expected to increase the tendency to produce mixtures when two oxygen sites are available, and this is clearly not the case.

The ultraviolet absorption spectra of the esters (XIV) showed α,β-unsaturated ketone absorption at wavelengths intermediate between those of the corresponding chalcones (XV and XVI). It was found

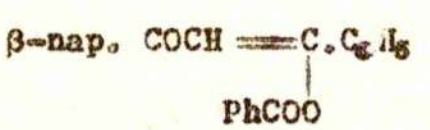


$$R_1.\underset{\substack{|\\ \text{OCOPh}}}{C}=CH.CO.R_2$$

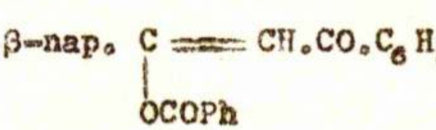
$R_1.CH=CH.CO.R_2$ $R_1.CO.CH=CH.R_2$

XIV XV XVI

that the ester absorption maximum was closer to that of the chalcone which contained the same conjugated system i.e., the ester XIV will resemble XV rather than XVI in its spectrum. This was extremely useful in assigning the correct structure to the ester without resorting to chemical means. Confirmation by hydrogenolysis was obtained in every case except that of the β-naphthyl compound, where the spectroscopic method indicated the structure XVII, while XVIII was actually correct. It was also



$$\beta\text{-nap}.\ COCH=\underset{\substack{|\\ \text{PhCOO}}}{C}.C_6H_5$$

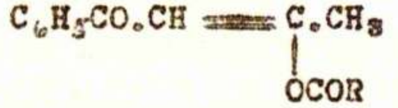


$$\beta\text{-nap}.\ \underset{\substack{|\\ \text{OCOPh}}}{C}=CH.CO.C_6H_5$$

XVII XVIII

found that the α-naphthyl ester showed no unsaturated ketone absorption in the ultraviolet (although this occurred as usual in the infrared), and the same applied to the impure ester obtained from mesitoylbenzoylmethane. Thus, the steric requirements of the naphthyl and mesityl groups apparently hinder the planarity required for complete conjugation in the esters; the β-isomer, as expected, has a smaller effect than the α-compound, and displaces the absorption to lower wavelengths (higher energy), in agreement with the idea of less complete conjugation. Provided no steric hindrance arises, this method is extremely convenient for assigning structures to the esters.

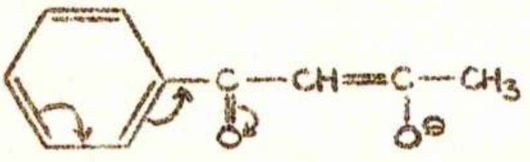
It was further observed that the maximum in the ester absorption spectrum was invariably closer to that ketone which absorbed at the lower wavelength of the two. Thus the ester contained the more stable resonance system. This could explain the absence of mixtures in the products, if the more thermodynamically stable isomer were preferred. However, in the case of benzoylacetone, the ester (XIX) does not contain the maximum conjugation and is therefore less stable than its isomer. The alternative explanation



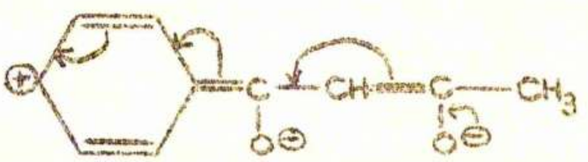
$$C_6H_5CO.CH = \underset{\substack{| \\ OCOR}}{C}.CH_3$$

XIX

is that the diketone reacts as the anion, and the more stable anion is exclusively preferred. In the cases of the diaroylmethanes, the more stable anion will be that which has the more stable unsaturated ketone resonance, and this is shown by the chalcone (XV or XVI) which absorbs at the lower wavelength. β-naphthoyl-benzoylmethane-O-benzoate contained the less stable resonance, but this is due to the steric interference between the naphthyl and ester groups. The charge on the anionic oxygen atom will then also be stabilised by cross-conjugation between the carbonyl group and the second aryl system. With benzoylacetone, the anion XX can be stabilised in this way (XXI), whereas the alternative structure cannot.

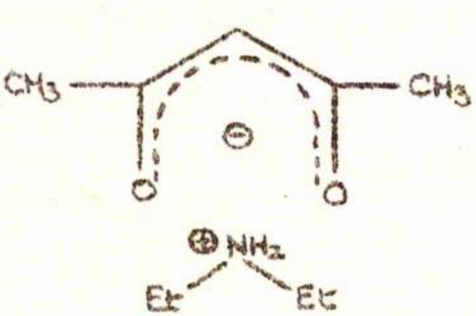


XX



XXI

The direct reactions between benzoyl chloride and the diketones had been carried out in pyridine. It was therefore thought possible that the basic nature of the medium could induce the formation of the enolate anion. A precedent for this had been given by the isolation[62], as an intermediate to Schiff base formation between acetylacetone and diethylamine, of a compound whose structure was shown by N.M.R. to be the ion-pair XXII.



XXII

Examination of pyridine/diketone mixtures by refractometry showed that a definite association occurred between the two molecules in a 1:1 ratio. The insolubility of the dibenzoylmethanes made it necessary to carry out these observations in dilute solution, and so only a slight deviation from Raoult's law may be observed. However, the liquid diketone dipivaloylmethane clearly shows the interaction.

It may therefore by concluded that esterification takes place by reaction of the enolate anion with benzoyl chloride or a benzoyl carbonium ion produced from it. The unsymmetrical diketones exclusively give the more stable anion, which is determined by resonance stabilisation of the negative charge, and also by unsaturated ketone conjugation, where this does not prevent the first condition.

The production of the same esters from the chelates as from the anion suggests either that the chelates have a separate ionic mechanism for O- acylation, or that there is considerable asymmetry in the metal-oxygen bonding. In view of the cumulative evidence in favour of a co-ordination mechanism for the chelate, the latter conclusion is more acceptable.

Isoxazole formation can therefore be taken as reflecting the properties of the chelated enol, which has a delicately balanced electron delocalisation within the enolic ring. In contrast, the esterifications show the behaviour of the enolate anion, which has a highly localised charge on one preferred oxygen centre.

CHAPTER 5

EXPERIMENTAL

Preparation of the Diketones

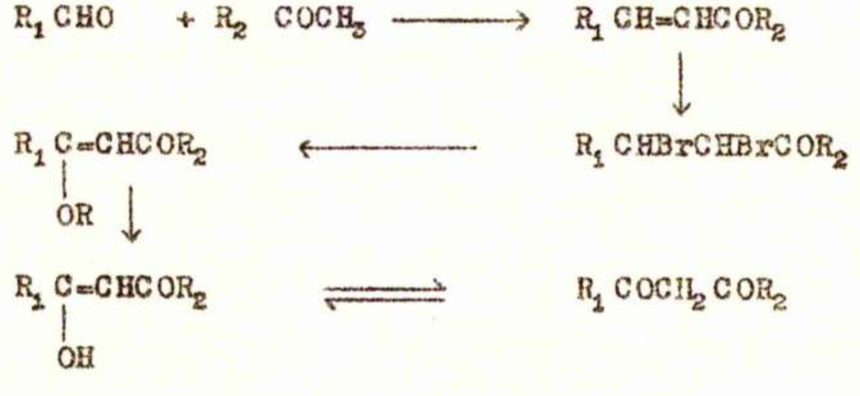
The diketones were generally obtained by one of the two methods described below.

A. By the Claisen condensation[101] of an ester with a methyl ketone, using sodamide or lithamide[48] as condensing agent:

$$R_1COCH_3 + R_2CO_2R \longrightarrow R_1COCH_2COR_2 + ROH$$

To a stirred suspension of the amide (2.5 moles) in ether was added the ketone (2 moles). The ester (1 mole) - usually the ethyl or phenyl ester - was gradually added as an ethereal solution, and the whole refluxed for a period of two to six hours. The slurry was poured onto ice, hydrochloric acid (50% aqueous) was added, and the whole shaken or stirred to hydrolyse the metal derivative. The ether layer was separated, washed with bicarbonate, water, dried and evaporated. The product was purified by crystallisation.

B From the appropriate αβ-dibromoketone, by treatment with sodium alkoxide, followed by acid hydrolysis of the resultant enol-ether:



$$R_1CHO + R_2COCH_3 \longrightarrow R_1CH{=}CHCOR_2$$

$$R_1CH{=}CHCOR_2 \longrightarrow R_1CHBrCHBrCOR_2$$

$$R_1CHBrCHBrCOR_2 \longrightarrow R_1\underset{\textstyle OR}{\underset{|}{C}}{=}CHCOR_2$$

$$R_1\underset{\textstyle OR}{\underset{|}{C}}{=}CHCOR_2 \longrightarrow R_1\underset{\textstyle OH}{\underset{|}{C}}{=}CHCOR_2 \rightleftharpoons R_1COCH_2COR_2$$

(i) Preparation of αβ-unsaturated ketones[102] ('chalcones').

To the methyl ketone (1 mole) in alcohol was added sodium or potassium hydroxide (0.1 mole as a 10% aqueous solution). After gradual addition of the aldehyde (1 mole), the solution was allowed to stand at room temperature, with stirring if required, for two to eighteen hours. The product separated, was filtered, and purified by crystallisation.

(ii) Bromination of the chalcones.[103]

The unsaturated ketone (1 mole) in solution (carbon tetrachloride or carbon disulphide) was treated with bromine (1 mole as 20% solution) at room temperature. The reaction time varied between two and eighteen hours. Any precipitate was filtered, washed, and the combined mother liquors and washings were freed from excess bromine by washing with aqueous sodium thiosulphate. The solution was concentrated and allowed to crystallise. The combined products were purified by recrystallisation.

(iii) Preparation of the diketone[104]

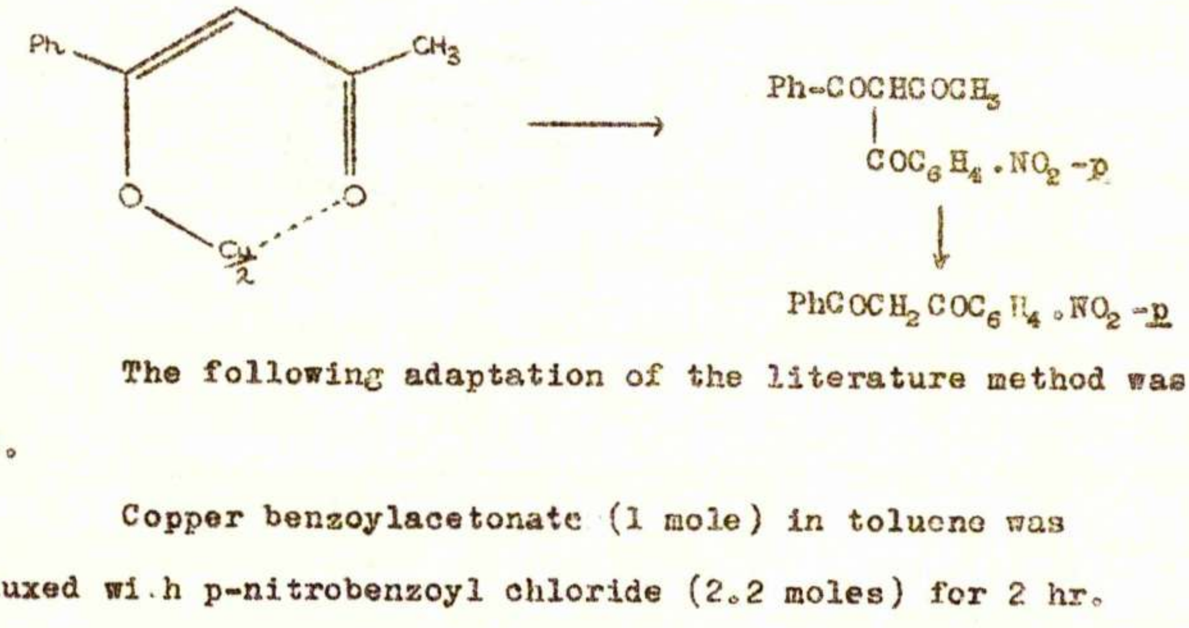
To a stirred suspension of the dibromide (1 mole) in alcohol was added a solution of sodium (2 moles) in alcohol. The mixture was refluxed (30 min.-3 hr.). A yellow solution of the enol ether was formed, and to this was added concentrated hydrochloric acid (0.2-0.3 moles), the mixture was refluxed for five minutes and poured into cold water. The product separated out and was filtered, or was extracted with ether. Purification was by recrystallisation.

By these methods, the following families of compounds were obtained.

Dibenzoylmethane was available as a laboratory reagent.

p-Nitrodibenzoylmethane.

This diketone was prepared[105] by reaction of the copper chelate of benzoylacetone with p-nitrobenzoyl chloride, followed by hydrolysis of the triketone obtained.

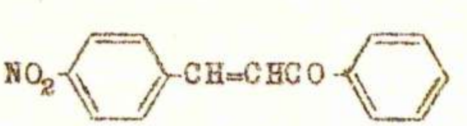


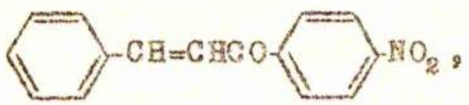
Ph-COCHCOCH_3 / $\text{COC}_6\text{H}_4\text{.NO}_2\text{-p}$

$\text{PhCOCH}_2\text{COC}_6\text{H}_4\text{.NO}_2\text{-p}$

The following adaptation of the literature method was used.

Copper benzoylacetonate (1 mole) in toluene was refluxed with p-nitrobenzoyl chloride (2.2 moles) for 2 hr. The solution was filtered, washed with dilute hydrochloric acid, bicarbonate, dried and evaporated. Ethanolic sulphuric acid (30% of concentrated acid) was added, and the mixture was heated on the water bath for 2 hr. The product separated on cooling, was filtered and crystallised from benzene as yellow needles, m.p. 162°.

4-nitrochalcone  , yellow prisms (benzene), m.p. 194°

4'-nitrochalcone  , yellow prisms (benzene), m.p. 146°.

4-nitrochalcone dibromide, colourless needles, m.p. 150-151° (from methanol-chloroform).

4'-nitrochalcone dibromide, colourless needles, m.p. 197-207° (chloroform).

p-Methoxydibenzoylmethane

Diketone, obtained by method A,[106] colourless plates, m.p. 133° (methanol).

4-Methoxychalcone, cream plates, m.p. 74-75° (ethanol).

Dibromide, colourless needles, m.p. 145° (benzene petrol).

4'-Methoxychalcone, colourless plates, m.p. 104-105° (ethanol).

Dibromide, colourless needles, m.p. 164° (benzene petrol).

p-Methyldibenzoylmethane

Diketone, obtained by method B, cream prisms, m.p. 84-85° (petroleum ether).

4-Methylchalcone, yellow needles, m.p. 93-94° (petroleum ether).

Dibromide, colourless needles, m.p. 165-167.5° (methanol/methylene chloride).

4'-Methylchalcone, colourless prisms, m.p. 55° (petroleum ether).

Dibromide, colourless prisms, m.p. 178-180° (ethanol/benzene).

p-Methoxy-p'-methyldibenzoylmethane.

Diketone, prepared by method B, cream prisms, m.p. 105° (methanol)

4-Methoxy-4'-methylchalcone, cream plates, m.p. 98-99° (methanol)

Dibromide, colourless prisms, m.p. 167-175° (benzene).

4'-Methoxy-4-methylchalcone, tiny colourless needles, m.p. 127-128° (methanol).

Dibromide, colourless prisms, m.p. 160-172° (benzene)

Mesitoylbenzoylmethane

Diketone, prepared by method B,[107] cream prisms, m.p. 80° (methanol).

2',4',6'-Trimethylchalcone, cream needles, m.p. 60° (methanol).

Dibromide, colourless prisms, m.p. 127° (carbon tetrachloride).

p-Bromodibenzoylmethane

Diketone, obtained by method B, colourless prisms, m.p. 90-92° (methanol).

4-Bromochalcone, pale yellow needles, m.p. 123.5-124°. (methanol).

Dibromide, colourless needles, m.p. 185° (benzene).

4'-Bromochalcone, pale yellow plates, m.p. 103-104° (methanol).

Dibromide, colourless prisms, m.p. 193° (carbon tetrachloride).

m-Bromodibenzoylmethane

Diketone, obtained by method B, cream prisms, m.p. 70° (petroleum ether) Found: C,59.93, H,4.10, Br,25.65% calc. for $C_{15}H_{11}BrO_2$: C,59.44, H,3.66, Br,26.36%.

3-Bromochalcone, cream needles, m.p. 87° (methanol).

Dibromide, colourless prisms, m.p. 154-157° (benzene/methanol). Found: C,40.12, H,2.76, Br,52.90; calc. for $C_{15}H_{11}Br_3O$: C,40.31, H,2.48, Br,53.64%.

3'-Bromochalcone, yellow needles, m.p. 94-94.5° (methanol)

Dibromide, colourless prisms, m.p. 132-133° (benzene/

methanol). Found: C,40.22, H,2.90, Br,52.20. calc. for $C_{15}H_{11}Br_3O$: C,40.31, H,2.48, Br,53.64%.

p-Chlorodibenzoylmethane.

Diketone, prepared by method B, pale yellow prisms m.p. 91-92° (petroleum ether).

4-Chlorochalcone, cream needles, m.p. 114-115° (ethanol).

Dibromide, white prisms, m.p. 177° (carbon tetrachloride).

4'-chlorochalcone, pale yellow needles, m.p. 98-99° (methanol).

Dibromide, colourless needles, m.p. 192° (carbon tetrachloride). Found: C,44.75, H,2.79. calc. for $C_{15}H_{11}Br_2ClO$. C,44.84, H,2.76%.

α-Naphthoylbenzoylmethane.

Diketone, prepared by method B, as impure yellow needles, m.p. 54.5-58.5° (ether/petroleum ether).

α-Naphthalacetophenone, yellow prisms, m.p. 88-89° (methanol).

Dibromide, in two forms: cream needles, m.p. 180° (carbon tetrachloride) and colourless needles, m.p. 132° (carbon tetrachloride).

α-Acetylnaphthalene, by Friedel-Crafts acetylation of naphthalene,[108] colourless liquid, b.p. 182° (20 mm.).

Benzal-α-acetylnaphthalene, clear yellow oil after chromatography on alumina.

Dibromide, colourless needles, m.p. 167-173° (benzene/petroleum ether).

β-Naphthoylbenzoylmethane.

Diketone, obtained by method B, pale yellow prisms, m.p. 102-103° (methanol/methylene chloride).

β-Naphthalacetophenone was obtained by reaction[109] of β-naphthaldehyde and acetophenone in dry ethyl acetate, using dry hydrogen chloride gas as catalyst. Yellow amorphous solid, m.p. 164° (benzene).

Dibromide, colourless needles, m.p. 190° (benzene).

Found: C, 54.56, H, 3.61, Br, 36.78. calc for $C_{19}H_{14}Br_2O$ C, 56.75, H, 3.51, Br, 39.76%.

β-Naphthyl styryl ketone, cream amorphous solid, m.p. 106-107° (ethanol).

Dibromide, cream needles, m.p. 174-175° (carbon tetrachloride).

Picolinylbenzoylmethane.

Diketone, obtained by method A, pale yellow prisms, m.p.

Furoylbenzoylmethane.

Diketone prepared by method A, cream prisms, m.p. 65° (petroleum ether).

The identity of the diketones was confirmed in every case by a positive ferric chloride test; by the formation of a coloured complex on mixing with aqueous copper acetate; and by the infrared absorption spectrum which showed hydrogen-bonded carbonyl absorption in the region 1580-1610 cm.$^{-1}$ (Nujol). All the diketones were shown to be 100% enolic by the absence of any free carbonyl absorption in the infrared.

All the chalcones showed characteristic αβ-unsaturated ketone absorption in the infrared (1652-1660 cm.$^{-1}$, Nujol) and in the ultraviolet (300-344 mμ, ethanol). These compounds also decolourised bromine solutions to form the dibromides, which showed saturated ketone absorption in the infrared (1683-1693 cm.$^{-1}$, Nujol).

Preparation of the Chelates

Copper. The copper chelates were prepared by addition of hot aqueous cupric acetate solution to a refluxing alcoholic solution of the diketone. The complex was filtered, washed with water and alcohol, and dried by the Dean and Stark method of azeotroping out the water by co-distillation with benzene or toluene.

These chelates were all highly insoluble, and were normally purified by elution with hot benzene or toluene. A few were capable of recrystallisation.

Copper dibenzoylmethide,[48] green needles (toluene), m.p. 316-317°.

Copper p-nitrodibenzoylmethide, green needles (DMF water, dried by D. and S.) m.p. 290° (dec.). Found: Cu, 10.60, calc. for $C_{30}H_{20}N_2O_8Cu$, Cu, 10.59%.

Copper p-methoxydibenzoylmethide, green needles (toluene), m.p. 239-244°. Found Cu, 11.12. calc. for $C_{32}H_{26}O_6Cu$, Cu, 11.16%.

Copper p-methyldibenzoylmethide, green needles (benzene/petrol) m.p. 241-245°. Found: Cu, 11.85. calc. for $C_{32}H_{26}O_4Cu$, Cu, 11.81%.

Nickel. The nickel chelates were prepared similarly, using nickel acetate. The majority of these complexes were soluble, and were purified by crystallisation.

Nickel dibenzoylmethide,[48] yellow-brown amorphous, m.p. 285-288° (elution with toluene).

Nickel p-nitrodibenzoylmethide, brown amorphous, m.p. 290° (dec.) (THF/water, dried by D. and S.). Found, Ni, 9.57 calc. for $C_{30}H_{20}N_2O_8Ni$, Ni, 9.86%.

Nickel p-methoxydibenzoylmethide, green amorphous, m.p. 256° (dec.) (toluene). Found: Ni, 10.16%; calc. for $C_{32}H_{26}O_6Ni$, Ni, 10.39%.

Nickel p-methyldibenzoylmethide, green amorphous, m.p. 288-292° (benzene/petrol). Found, Ni,10.55%. calc. for $C_{32}H_{26}O_4Ni$, Ni,11.01%.

Nickel p-methoxy-p'-methyldibenzoylmethide, yellow amorphous, m.p. 283-289 (dec.) would not hydrolyse quantitatively for analysis.

Nickel p-chlorodibenzoylmethide, green amorphous, m.p. 284-286° (dec.) (benzene/petrol). Found: Ni,9.77. calc. fc $C_{30}H_{20}Cl_2O_4Ni$, Ni,10.19%.

Nickel p-bromodibenzoylmethide, green amorphous, m.p. 265° (dec.)(elution with benzene). Found: Ni,8.10. calc. for $C_{30}H_{20}Br_2O_4Ni$, Ni,8.83%.

Nickel m-bromodibenzoylmethide, yellow-green amorphous, m.p. 270° (dec.) (benzene/petrol). Found: Ni,8.62%. calc. for $C_{30}H_{20}Br_2O_4Ni$, Ni,8.83%.

Sodium. Sodium dibenzoylmethide[48] was prepared by addition of sodium hydroxide (40% aqueous solution) to a solution of the diketone in acetone. The chelate was precipitated as pale yellow needles by addition of petroleum ether, was filtered and dried by the Dean and Stark method. Pale yellow needles, m.p. > 340°.

Sodium p-nitrodibenzoylmethide was obtained pure by addition of methanol to a stirred suspension of sodium hydride (50% dispersion in oil) in a toluene solution of the diketone. The precipitate was filtered, washed with methanol and toluene, and dried. Orange-yellow amorphous solid, m.p. > 340°. Found: Na,7.91. calc. for $C_{15}H_{10}NO_4Na$, Na,7.90%.

Sodium p-methoxydibenzoylmethide was formed by refluxing a dry toluene solution of the diketone with powdered sodamide. The chelate was filtered off and was extracted from the inorganic residues with ethyl acetate. The pure chelate was obtained by evaporation of this solution. Pale yellow amorphous solid, m.p.> 340°. Found: Na,8.44. calc. for $C_{16}H_{12}O_3Na$, Na,8.32%.

Sodium p-methyldibenzoylmethide was obtained and purified in the same way as the methoxy-analogue. Pale yellow amorphous solid, m.p.>340°. Found: Na,8.70, calc. for $C_{16}H_{12}O_2Na$, Na,8.83%.

Barium. Barium dibenzoylmethide[48] was prepared by addition of aqueous barium hydroxide to a solution of dibenzoylmethane in acetone. The chelate was dried by D. and S. and purified by elution with hot toluene. Yellow amorphous solid m.p. > 340°.

Barium p-nitrodibenzoylmethide could best be obtained by refluxing the diketone in pyridine with finely powdered barium hydroxide, in presence of a trace of water, for half an hour. The solution was filtered and evaporated to dryness. After washing with petroleum ether, the product was recrystallised (DMF/water), and dried by D. and S. Orange-red needles, m.p. 294-296° (DMF/water). Found, Ba,20.38 calc. for $C_{30}H_{20}N_2O_8Ba$, Ba,19.89%.

Barium p-methoxydibenzoylmethide could only be obtained as an impure yellow solid, m.p. 268-285°. Analysis indicated a high inorganic impurity content, and the chelate could not be purified further.

Zinc. Zinc dibenzoylmethide[48] was formed by addition of aqueous zinc acetate to an alcoholic solution of dibenzoylmethane. Dried by D. and S., crystallised from toluene/petrol. Yellow prisms, m.p. 211-213°.

Zinc p-nitrodibenzoylmethide was prepared in the same manner, but addition of dilute ammonia was required to form the chelate. Crystallised from ethyl acetate/DMF, orange needles, m.p. 255-260°. Found, Zn, 10.71. calc. for $C_{30}H_{20}N_2O_8ZN$, Zn, 10.86%.

Zinc p-methoxydibenzoylmethide could only be prepared by 'double decomposition' of the sodium chelate with zinc chloride in acetone. Addition of excess water caused precipitation of the chelate, which was filtered and dried over phosphorus pentoxide (in vacuo). Heating of the chelate in presence of water caused hydrolysis. The dry chelate was recrystallised from toluene as yellow prisms, m.p. 192-194°. Found: Zn, 10.77. calc. for $C_{32}H_{28}O_6Zn$, Zn, 11.43%.

UV Spectra ($\lambda_{max.}$, mμ.) of diketones and chelates ($CHCl_3$).

Diketone	H	Cu	Ni	Na	Ba	Zn
Dibenzoylmethane	251	261	250	251	250	253
	344	350	350	340	343	340
p-Nitro-dibenzoylmethane	262	290	263	267	261	266
	358	362	359	360	360	362
p-Methoxy-dibenzoylmethane	293	232	284	258	228	226
	357	357	361	357	357	356
p-Methyl-dibenzoylmethane	245	271	256	254	-	-
	347	352	352	348	-	-

The infrared spectra of all the chelates showed no free carbonyl absorption, but gave the characteristic 'chelate carbonyl' absorption at 1590-1600 cm.$^{-1}$

Preparation of the Enol-esters.

Esterification of the diketones was carried out directly, or by reaction of a metal chelate with the acid chloride.

(a) From the Diketone.

To the diketone (1 mole), in the minimum volume of anhydrous pyridine, was added benzoyl chloride (1.2 moles) at room temperature. Reaction occurred (3-18 hr.) with evolution of heat and precipitation of pyridinium hydrochloride. After completion of the reaction, water (2-3 drops) was added to give a homogeneous solution; on standing (20-30 min.), hydrolysis of excess acid chloride took place. The solution was diluted with excess water, extracted with ether, and the organic layer freed from pyridine by washing with aqueous mineral acid. After further washing with bicarbonate and water, the ethereal solution was dried and evaporated. The products were generally obtained as oils which could be solidified by freezing and treatment with petroleum ether. Chromatography on alumina was occasionally require to remove traces of diketone and other impurities. The products were finally purified by recrystallisation.

(b) From the Chelates.

A solution or suspension of the chelate (1 mole) was refluxed with benzoyl chloride (2.2 moles) until the characteristic colour of the chelate disappeared. After removal of the metal chloride by filtration, the solution was cooled and a few c.c.s. of pyridine added, along with a trace of water. When hydrolysis was complete ($\frac{1}{2}$-2 hr.), the solution was washed with acid, bicarbonate and water. Any triketone was removed by fractional crystallisation, and the residues were crystallised directly, or chromatographed on alumina, to yield the enol-benzoate.

In every case, one isomer was the sole product, as shown by melting point, infrared and ultraviolet spectra. The compounds gave no colour with ferric chloride, showed αβ-unsaturated ketone absorption frequencies in the ultraviolet

(300-327 mμ, methanol), and in the infrared gave ester carbonyl (1730-1745 cm.$^{-1}$), αβ-unsaturated carbonyl (1660-1670 cm.$^{-1}$) and double bond (1587-1620 cm.$^{-1}$) absorption frequencies (Nujol).

p-Nitrodibenzoylmethane-O-benzoate, yellow needles, m.p. 155° (toluene). Found: C, 70.80, H, 4.05, N, 3.56. calc. for $C_{22}H_{15}NO_5$, C, 70.77, H, 4.05, N, 3.75%.

p-Methoxydibenzoylmethane-O-benzoate, pale yellow prisms, m.p. 98-99° (petroleum ether). Found: C, 77.31, H, 5.11. calc. for $C_{23}H_{18}O_4$, C, 77.08, H, 5.06%.

p-Methyldibenzoylmethane-O-benzoate, pale yellow prisms, m.p. 102-103° (benzene/petroleum ether). Found: C, 81.04, H, 5.41. calc. for $C_{23}H_{18}O_3$, C, 80.68, H, 5.30%.

p-Methoxy-p'-methyldibenzoylmethane-O-benzoate, pale yellow needles, m.p. 129.5-130° (benzene/petroleum ether). Found: C, 77.24, H, 5.62% calc. for $C_{24}H_{20}O_4$, C, 77.40, H, 5.41%.

p-Bromodibenzoylmethane-O-benzoate, pale yellow needles, m.p. 122-123° (benzene/petroleum ether). Found: C, 64.62, H, 3.94. calc. for $C_{22}H_{15}BrO_3$, C, 64.86, H, 3.71%.

p-Chlorodibenzoylmethane-O-benzoate, yellow needles (ether) m.p. 98-100°. Found: C, 73.97, H, 4.67, Cl, 9.90. calc. for $C_{22}H_{15}ClO_3$, C, 72.80, H, 4.36, Cl, 9.90%.

m-Bromodibenzoylmethane-O-benzoate, yellow amorphous, m.p. 100° (benzene/petroleum ether). Found: C, 64.97, H, 3.57. calc. for $C_{22}H_{15}BrO_3$, C, 64.86, H, 3.71%.

Mesitoylbenzoylmethane-O-benzoate, yellow oil. Found: C,80.15, H,5.82, calc. for $C_{25}H_{22}O_3$, C,81.04, H,5.99%.

α-Naphthoylbenzoylmethane-O-benzoate, pale yellow needles, m.p. 129.5-130° (ether). Found: C,82.82, H,4.97. calc. for $C_{26}H_{19}O_3$, C,82.52, H,4.79%.

β-Naphthoylbenzoylmethane-O-benzoate, pale yellow needles, m.p. 150-151° (benzene). Found: C,82.20, H,5.20. calc. for $C_{26}H_{19}O_3$, C,82.52, H,4.79%.

Furoylbenzoylmethane-O-benzoate, yellow amorphous, m.p. 137-139° (benzene/petroleum ether). Found: C,75.40, H,4.77. calc. for $C_{20}H_{14}O_4$, C,75.46, H,4.43%.

The triketone derived from the chelate reactions of p-nitrodibenzoylmethane itself formed an enol-benzoate.

p-nitrotribenzoylmethane-O-benzoate, white needles, m.p. 167-168° (benzene/petroleum ether). Found: C,73.46, H,4.24, N,2.78% calc. for $C_{29}H_{19}NO_6$, C,72.95, H,4.01, N,2.93%.

Preparation of the Triketones.

Two methods were again used to obtain the C-benzoylated diketones, the first using the Claisen procedure,[110] and the second utilising the reactions of the chelates.

(a) From the Diketone.

To the diketone (1 mole) in alcohol was added an alcoholic solution of sodium (1 mole). The mixture was warmed to 60°, and benzoyl chloride (1 mole) was added with stirring. The triketone separated on cooling. Concentration of the mother liquor, and further treatment with sodium (0.5 moles) and benzoyl chloride (0.5 moles) gave a further yield of product. The triketones were purified by recrystallisation.

(b) From the Chelates.

The C-compounds were formed, along with the enol-esters, in the acylation reactions of the metal chelates. The procedure was similar to that used to prepare the esters, but the triketones were obtained directly by recrystallisation of the reaction products, or by alkali extraction.

These compounds existed in part as the enolic modifications and the proportion of the equilibrium mixture wad dependent on the solvent from which the product was crystallised. This fact was reflected in the variable range of melting points obtained. Generally, the compounds gave positive ferric chloride tests, formed chelates with copper acetate, and showed both saturated (ca.1695 cm.$^{-1}$) and αβ-unsaturated (ca.1670 cm.$^{-1}$) carbonyl absorption frequencies in the infrared.

p-Nitrotribenzoylmethane, colourless plates, m.p. 160-210° (benzene).

p-Methoxytribenzoylmethane, colourless needles, m.p. 213° (acetone).

p-Methyltribenzoylmethane, colourless needles, m.p. 204-205° (methanol). Found: C,81.33, H,5.49. calc. for $C_{23}H_{18}O_3$, C,80.68, H,5.30%.

p-Methoxy-p'-methyltribenzoylmethane, colourless needles, m.p. 188-195° (benzene). Found: C,77.07, H,5.91. calc. for $C_{24}H_{20}O_4$, C,77.40, H,5.41%.

p-Bromotribenzoylmethane, colourless needles, m.p. 165-170° (benzene/petroleum ether)

p-chlorotribenzoylmethane, colourless needles, m.p. 190-197° (benzene/petroleum ether). Found: C,72.82, H,4.41, Cl,10.56. calc.for $C_{22}H_{15}ClO_3$. C,72.80, H,4.36, Cl,9.77%.

m-Bromotribenzoylmethane, colourless needles, m.p. 190-220° (benzene/petroleum ether).

Reactions of the Chelates

The chelate (1 mole) as a 2% solution or suspension in anhydrous benzene, was refluxed until the maximum degree of homogeneity was obtained. To the boiling mixture was added benzoyl chloride (2.2 mole, 1.1 moles for the sodium chelates), and the whole was refluxed until the last trace of chelate colour had disappeared.

The solution was filtered hot to remove the inorganic product, cooled, and pyridine and a trace of water were added to hydrolyse excess acid chloride. After hydrolysis (½ - 2 hr.)

the organic solution was washed with aqueous hydrochloric acid to remove pyridine, and with sodium bicarbonate solution to remove benzoic acid.

Estimation of the Product Ratio.

The method of ultraviolet analysis,[48,99] which had previously been used to determine the proportions of O- and C-acylated products, was found to be unreliable for the systems under examination. The existence of keto-enol equilibria in the structures of the triketones gave an effective total of four components (diketone, enol ester and two forms of triketone) in the reaction products, and the above method is applicable only to two- or three-component systems. A wide range of tests of the method were carried out on known mixtures of the expected products, and these showed that the calculated figures were only accurate for high proportions of triketone (above 80%). Other mixtures gave inaccurate results, and actual reactions gave figures which could not be verified by physical or chemical separation techniques.

The enol-forms of the triketones were found to be sufficiently acidic to be extracted by dilute sodium hydroxide, leaving the less acidic diketone in the organic solution. In the case of the nitro series, the diketone was also soluble in the alkali, but the C-compound could be separated by sodium carbonate solution.

Conversion of the residual ketonic isomer to the enol was effected by warming with methanolic sodium hydroxide.

An equilibrium was found to exist and the conversion process was repeated several times until all the C-compound was extracted. The following procedure was developed.

The benzene solution of the reaction products was diluted with petroleum ether, then extracted with alkali (2% aqueous sodium hydroxide) until no further colour entered the aqueous layer. The organic solution was dried and evaporated and the residue dissolved in methanol; a little aqueous sodium hydroxide was added, and the whole heated on the water-bath for 5 min. Ethyl acetate was added, and the solution extracted as before. This procedure was repeated (up to 4 times) until no further colour could be extracted into the water layer. The combined extracts were acidified and the resultant precipitate dissolved in methylene chloride. After removal of benzoic acid by washing with bicarbonate, the solution was evaporated, and the product weighed.

In the case of the chelates of p-nitrodibenzoylmethane, the O-benzoate of the triketone was separated out and purified by fractional crystallisation. The residues were treated as above, but extraction was effected by sodium carbonate solution.

The proportion of C-acylation was calculated from the combined ester and alkaline extract yields.

The enol-esters of the diketones, on treatment with methanolic alkali as above, were converted almost quantitatively into the diketones, identified by melting point, mixed melting point and infrared spectra.

The triketones were found to be virtually unaffected by the alkali treatment.

No isomerisation of the O-compounds could be detected either on treatment as above, or on heating with the corresponding sodium chelate.

The accuracy of the method is demonstrated by the results of the following tests.

(a) A mixture of p-methoxytribenzoylmethane (0.438 g.) and p-methoxydibenzoylmethane (0.415 g.) was dissolved in benzene and treated as above. The alkaline extract was a white solid (0.413 g.) identified as the triketone by m.p. and mixed m.p. (205°) and by the infrared spectrum. Thus the actual and experimental proportions of C-compound were 46.2% and 43.5% respectively.

(b) Tribenzoylmethane (0.0444 g.) and dibenzoylmethane (0.0518 g.) were tested in the same way. Extraction gave tribenzoylmethane (0.0424 g.), identified by melting point and infrared spectrum.

The actual proportion of C-compound was 46.1%, the experimental figure 44.0%.

The chelate reactions were carried out in duplicate, and if necessary were repeated until the results were consistent to within 5% of each other.

Percentages of C-benzoylation and reaction times of chelates of substituted dibenzoylmethanes in benzene.

(* indicates heterogeneous reaction mixture).

	Copper	Nickel	Sodium	Barium	Zinc
p-NO_2	22.4, 18.0 *55 hr.	2.5, 2.4 *1 hr.	20.6, 20.6 *2 hr.	37.3, 33.4 * 2 hr.	13.9, 8. 1½ hr
p-H	24.2, 22.5 *3 days	38.1, 34.0 *10 min.	32.3, 34.4 *3 hr.	30.7, 28.5 * 45 min.	8.8, 8. 10 min
p-CH_3O	22.1, 22.1 *20 hr.	43.0, 38.9 5 min.	29.1, 29.1 *10 min		12.2, 13 5 min
p-CH_3	60.9, 59.3 *20 hr.	65.1, 61.0 10 min.	58.4, 57.1 * 6 hr.		

Percentages of C-benzoylation and reaction times of nickel chelates of substituted dibenzoylmethanes in benzene.

(* indicates heterogeneous reaction mixture).

p-NO_2	m-Br	p-Br	p-Cl	p-H	p-CH_3O	p-CH_3O p-CH_3	p-CH_3
2.5	24.4	25.2	27.7	38.1	43.0	46.0	65.1
2.4	20.8	26.7	31.0	34.0	38.9	48.3	61.0
*1 hr.	10 min.	5 min.	5 min.	*10 min.	5 min.	*30 min.	10 min.

Reaction of Copper p-Nitrodibenzoylmethide with Benzoyl Chloride

The chelate (1.00 gm.) in anhydrous benzene (50 ml.) was refluxed with benzoyl chloride (0.45 ml.) until no further reaction was observed (55 hr.). Ethyl acetate was added to completely dissolve the organic product, and the solution was filtered hot. The residue (0.65 gm.) was crystalline (small needles) and yellow in colour, m.p. 290-330°. This product was not the expected cuprous chloride, but a copper-containing complex. Analysis showed Cu, 15.35%, agreeing best with a structure Cl-Cu-(diketone) (Cu, 17.70%).

Reactions of the Complex.

1. Hydrolysis of the complex (0.391 gm.) with aqueous methanolic sulphuric acid gave, as organic product, p-nitrodibenzoylmethane (0.284 gm.) identified by m.p. 162° and mixed m.p., and by its infrared spectrum. Chloro-copper-diketone (0.391 g.) would yield 0.286 gm. of diketone. The inorganic product contained cupric copper, as shown by the liberation of iodine from potassium iodide, and by its formation of a deep blue colour with ammonia.

2. Addition of ammonium hydroxide to an aqueous suspension of the complex gave no colouration, even on warming. Thus, no free copper ion was present.

3. Refluxing of the complex with water (20 hr.) gave a pale blue aqueous solution which, on addition of potassium iodide, gave a yellow colour which turned deep blue with starch solution; on addition of ammonia gave a deep blue colour; and on addition of silver nitrate solution gave a white precipitate of silver chloride. Thus, cupric chloride was formed in the reaction.

$$2\ ClCu(DK) \longrightarrow CuCl_2 + Cu(DK)_2$$

Hydrogenation of the Enol-Esters[91]

To a solution of the ester in ethyl acetate was added Adams platinum oxide catalyst (5% or 10% of the weight of ester), and hydrogenation was carried out at room temperature and pressure, with vigorous stirring. The compounds generally absorbed more than the theoretical two moles of hydrogen, and the reactions were stopped after 2¼-2½ moles had been taken up. The catalyst was filtered off, and the solution washed with bicarbonate to remove benzoic acid. Evaporation of the solution usually gave an oily product which was purified by crystallisation or, more often, by chromatography on alumina. In some cases the crude product had to be directly converted into the dinitrophenylhydrazone.

If all or part of the desired ketone had been hydrogenated to the secondary alcohol, as was occasionally found, regeneration of the carbonyl compound was accomplished by oxidation with chromic acid (8N chromium trioxide in aqueous mineral acid). This reaction took place at room temperature on shaking an acetone solution of the alcohol with a slight excess (10%) of chromic acid for a few minutes. The excess reagent was destroyed with sodium bisulphite, and the organic product extracted with ether.

Hydrogenation of the Chalcones.

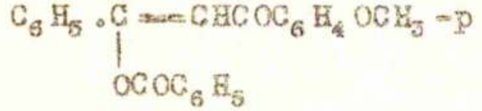
The appropriate αβ-unsaturated ketone was hydrogenated to the saturated compound by the same procedure as was used for the esters, without requiring removal of benzoic acid from the reduction product. Hydrogen uptake was stopped at the theoretical level (one mole), and there was seldom any alcohol formed. The ketones were purified directly, or converted into suitable derivatives.

In this way, the structures of the following series of esters were proven.

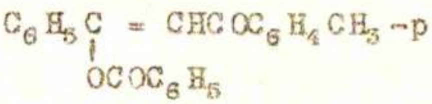
p-Nitrodibenzoylmethane-O-benzoate gave no identifiable hydrogenation product; a crude oil which could not be purified was the only product, besides benzoic acid.

4-Nitrochalcone gave β-(p-aminophenyl)-propiophenone p-$NH_2C_6H_4CH_2CH_2COC_6H_5$, colourless needles (petroleum ether) m.p. 78.5-80°. Found: C, 79.98, H, 6.81, N, 5.80. calc. for $C_{15}H_{15}NO$, C, 79.97, H, 6.71, N, 6.22%.

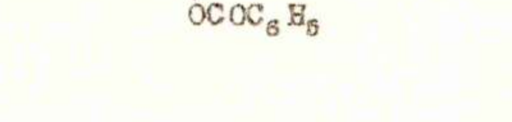
p-Methoxydibenzoylmethane-O-benzoate gave β-phenyl-p-methoxypropiophenone $C_6H_5CH_2CH_2COC_6H_4OCH_3$-p as colourless plates (methanol), m.p. 95-96°. This product was identical with a sample obtained from 4'-methoxychalcone. Thus the ester is


$C_6H_5.\underset{\substack{|\\ OCOC_6H_5}}{C}=CHCOC_6H_4OCH_3\text{-p}$

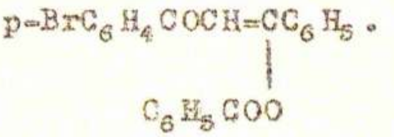
p-Methyldibenzoylmethane-O-benzoate gave β-phenyl-p-methylpropiophenone p-$CH_3C_6H_4COCH_2CH_2C_6H_5$ as colourless plates, m.p. 68°. This was identical with the product obtained from 4'-methylchalcone. Thus the ester is


$C_6H_5\underset{\substack{|\\ OCOC_6H_5}}{C}=CHCOC_6H_4CH_3\text{-p}$

p-Methoxy-p'-methyldibenzoylmethane-O-benzoate gave an oil, converted into its DNP, orange needles (benzene), m.p. 201-202°. This was identified as the DNP of β-(p-tolyl)-p-methoxypropiophenone, obtained from 4-methyl-4'-methoxychalcone. The DNP was analysed: Found: C, 63.51, H, 5.41, N, 12.78. calc. for $C_{23}H_{22}N_4O_6$, C, 63.58, H, 5.10, N, 12.90%. The ester has the structure

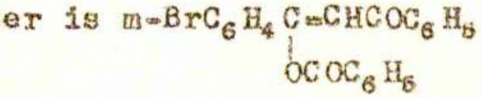

$\text{p-}CH_3C_6H_4\underset{\substack{|\\ OCOC_6H_5}}{C}=CHCOC_6H_4OCH_3\text{-p}$

<u>p-Bromodibenzoylmethane-O-benzoate</u> gave β-phenyl-p-bromopropiophenone as colourless plates (petroleum ether), m.p. 101°, identical with the product from 4'-bromochalcone. Found: C,62.60, H,4.76, Br,27.84. calc. for $C_{15}H_{13}BrO$, C,62.30, H,4.53, Br,27.64% The ester is



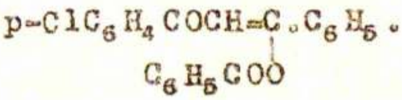
$$p\text{-}BrC_6H_4COCH{=}\underset{\displaystyle C_6H_5COO}{C}C_6H_5$$

<u>m-Bromodibenzoylmethane-O-benzoate</u> gave a yellow oil, converted to the DNP, identified as that of β-(m-bromophenyl)-propiophenone, obtained from 3-bromochalcone. The DNP was obtained as orange needles (benzene petroleum ether) m.p. and mixed m.p. 202-203°. Found: C,53.22, H,3.85, N,11.95. calc. for $C_{21}H_{16}N_4BrO_4$, C,53.73, H,3.65, N,11.93%. The ester is



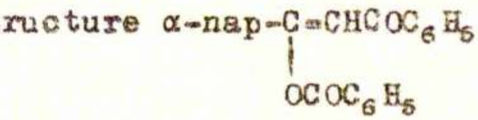
$$m\text{-}BrC_6H_4\underset{\displaystyle OCOC_6H_5}{C}{=}CHCOC_6H_5$$

<u>p-Chlorodibenzoylmethane-O-benzoate</u> gave 4'-chlorochalcone, identified by m.p. and mixed m.p., and by infrared and ultraviolet spectra. Thus the ester is



$$p\text{-}ClC_6H_4COCH{=}\underset{\displaystyle C_6H_5COO}{C}.C_6H_5$$

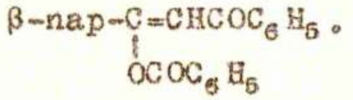
<u>α-Naphthoylbenzoylmethane-O-benzoate</u> gave α-naphthalacetophenone, identified as the DNP - red needles (benzene) m.p. and mixed m.p. 223-230°. The ester has the structure



$$\alpha\text{-}nap\text{-}\underset{\displaystyle OCOC_6H_5}{C}{=}CHCOC_6H_5$$

<u>β-Naphthoylbenzoylmethane-O-benzoate</u> gave β-(β-naphthyl)-propiophenone, identified as the DNP from the hydrogenation

of β-naphthalacetophenone. The derivative crystallised from benzene as red needles, m.p. and mixed m.p. 236°. Found: C, 68.24, H, 4.44, N, 12.31. calc. for $C_{25}H_{20}N_4O_4$, C, 68.17, H, 4.58, N, 12.72%. A second hydrogenation of the ester gave β-naphthalacetophenone, confirming the structure as



$$\beta\text{-nap-}\underset{\mathrm{OCOC_6H_5}}{\mathrm{C}}\mathrm{=CHCOC_6H_5}.$$

The enol esters of α-naphthoylbenzoylmethane and mesitoylbenzoylmethane showed no αβ-unsaturated ketone absorption in the ultraviolet, but in the infrared absorbed at 1674 and 1679 cm.$^{-1}$, respectively, showing some degree of αβ-unsaturation.

Ultraviolet Absorption of αβ-unsaturated ketones in Enol Esters and Related Chalcones ($\lambda_{max.}$ mμ, methanol).

(DBM ≡ dibenzoylmethane)

Parent Diketone	ArCOCH=CHPh	ArCH=CHCOPh	Enol Ester	Structure of Ester
p-NO_2 DBM	313	306	306	ArC=CHCOPh OCOPh
p-CH_3 ODBM	312	334	313	ArCOCH=CPh PhCOO
p-CH_3 DBM	310	323	311	ArCOCH=CPh PhCOO
p-CH_3 O-p'-CH_3 DBM	CH_3O CH_3 327	344	327	CH_3O CH_3 ArCOCH=CPh PhCOO
p-ClDBM	314	316	312	ArCOCH=CPh PhCOO
p-BrDBM	314	318	310	ArCOCH=CPh PhCOO
m-BrDBM	314	300	300	ArC=CHCOpH OCOPh
α-Naphthoyl BM	305	355		ArC=CHCOPh OCOPh
β-Naphthoyl BM	316	327	317	ArC=CHCOPh OCOPh
Furoyl BM	320	344	329	ArCOCH=CPh PhCOO
Picolinyl BM	318	303		ArC=CHCOPh OCOPh

Preparation of β(α)-bromo-4-nitrochalcone.[103]

4-Nitrochalcone dibromide (10.9 g.) and anhydrous potassium acetate (3.2 g.) were refluxed in methanol (100 ml.) for 42 hr. The solution was filtered free of potassium bromide, concentrated and diluted with water. The product was extracted with ether, washed with aqueous sodium bicarbonate, dried and evaporated to yield an orange-coloured oil (7.7 g.). A Lassaigne test confirmed the presence of bromine, and the infrared spectrum showed αβ-unsaturated carbonyl (1667 cm.$^{-1}$) and double bond (1589 cm.$^{-1}$) absorption, confirming the structure. The oil would not crystallise, but the infrared spectrum showed a high degree of resolution and purity.

Attempted reaction of bromo-4-nitrochalcone with silver benzoate.

A solution of bromo-4-nitrochalcone (3.85 g.) in anhydrous benzene was added to a suspension of silver benzoate in the same solvent. After an extended period of reflux (70 hr.), the mixture was filtered. The residue was completely soluble in concentrated ammonia, i.e. it was unreacted silver benzoate. Evaporation of the benzene solution gave an oil, identified as unreacted bromo-chalcone by the infrared spectrum.

Preparation of β(α)-bromo-(β-naphthyl styryl ketone).[72]

β-Naphthyl styryl ketone dibromide was dissolved in pyridine and heated on the water bath for 5 min. The solution was poured into water, extracted with ether, and the extract washed with dilute hydrochloric acid. Evaporation gave a yellow oil which solidified and was purified by crystallisation from petroleum ether as colourless needles, m.p. 116°. The structure was confirmed by the infrared and ultraviolet spectra. The N.M.R. spectrum showed a doublet at 1.6, 1.76τ, corresponding to a single proton.

The N.M.R. of β-naphthyl styryl ketone itself showed a broad unresolved peak at 1.47τ, corresponding to one proton. Since the β-proton of the system -CH=CH-C=O normally appears further downfield than the α-proton, this absorption (1.47τ) must be that due to the β-proton, and the signal from the α-hydrogen must be concealed by the aromatic region of the spectrum (1.9-2.8τ).

Thus the monobromochalcone must also have a β-proton, and the structure is α-bromo-(β-naphthyl styryl ketone) $C_{10}H_7COCBr{=}CHC_6H_5$.

Interaction of Pyridine and the Diketones.

Mixtures of pyridine and acetylacetone, and pyridine and benzoylpivaloylmethane; and also solutions in toluene of pyridine/p-methyldibenzoylmethane and pyridine/dibenzoylmethane, were prepared, and then refractive indices measured using an Abbé refractometer. Curves of mole fraction: n^2 (n=refractive index) were drawn. The results are shown below.

Refractive Indices of Mixtures of Pyridine and Acetylacetone

Mole % pyridine	0	16.81	25.83	33.20	76.88	81.60	88.84	100
Refractive Index n	1.4478	1.4547	1.4590	1.4627	1.4873	1.4906	1.4959	1.5030
n^2	2.096	2.115	2.128	2.139	2.212	2.222	2.238	2.259

Refractive Indices of Mixtures of Pyridine and Benzoylpivaloylmethane

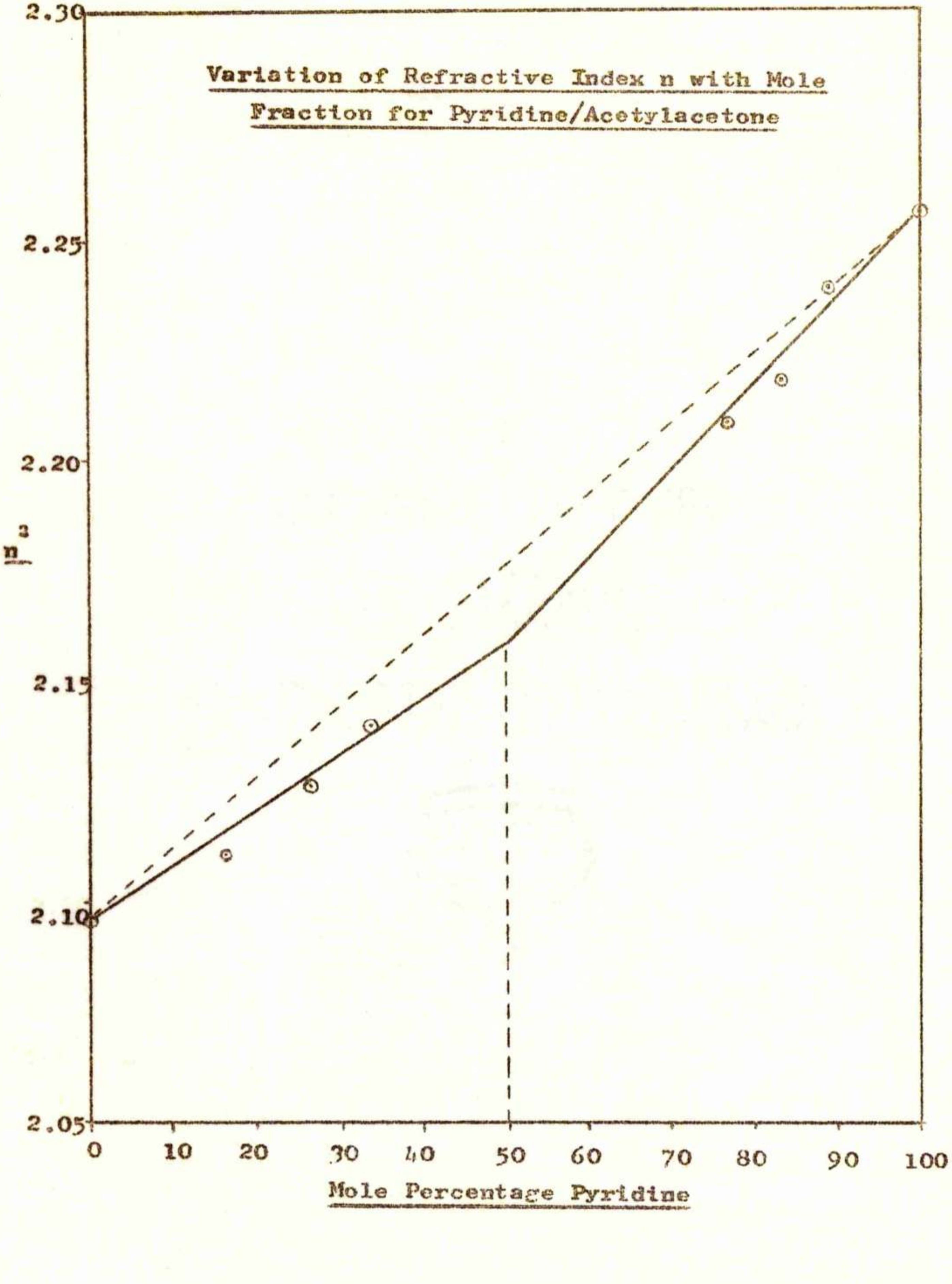
Mole % pyridine	0	14.25	24.19	50.00	40.60	48.61	100	-
n	1.5647	1.5610	1.5580	1.5482	1.5520	1.5485	1.5070	-
n^2	2.4481	2.4367	2.4271	2.3964	2.4077	2.3981	2.2707	-

Refractive Indices of 0.1 Molar Pyridine/pCH_3 DBM mixtures in Toluene

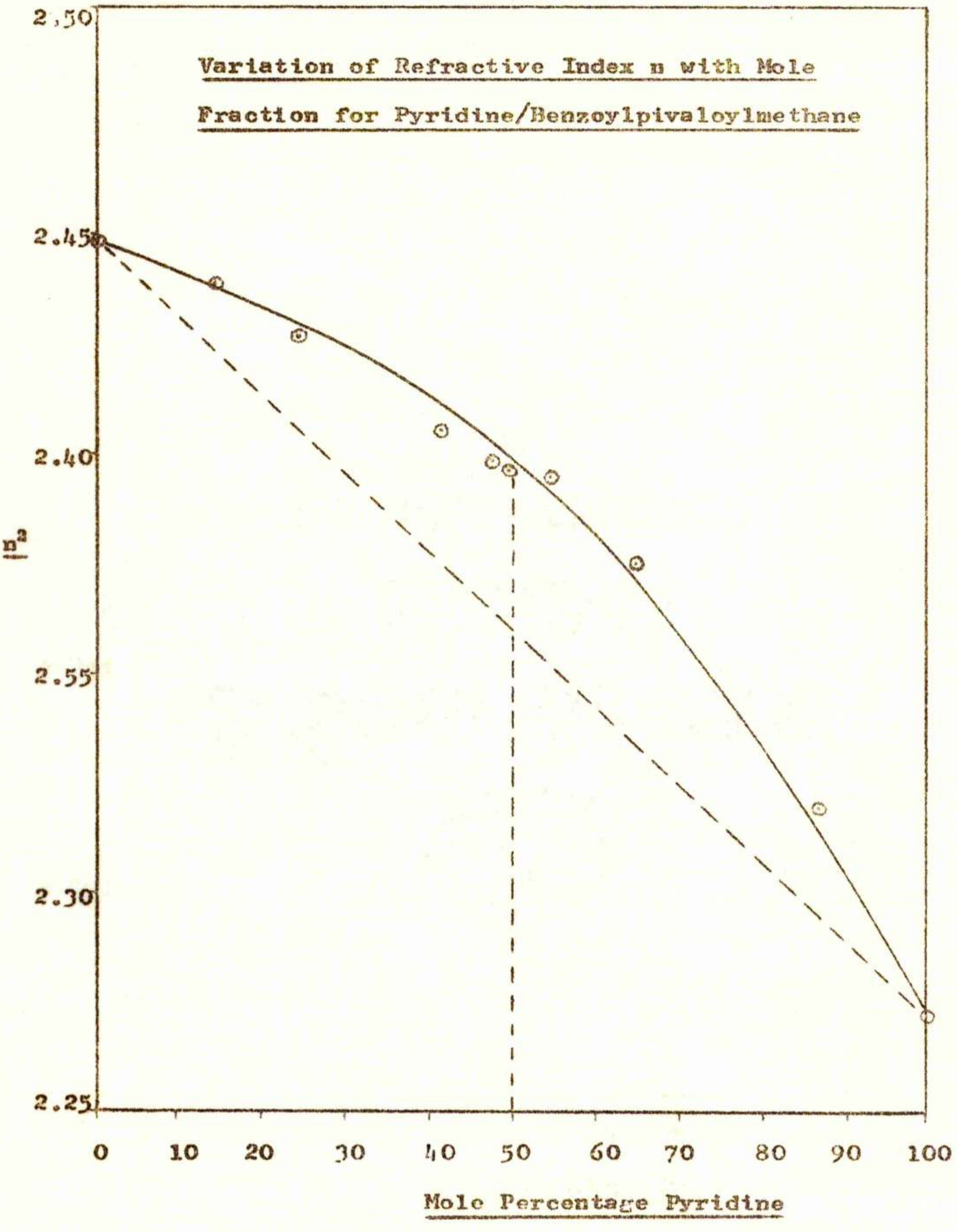
Mole % pyridine	0	20	30	40	50	60	70	80	100
Refractive Index n	1.5022	1.5010	1.5003	1.4999	1.4993	1.4988	1.4983	1.4979	1.4969
n^2	2.2565	2.2530	2.2511	2.2498	2.2483	2.2468	2.2454	2.2441	2.2410

Refractive Indices of Pyridine/Dibenzoylmethane Mixtures as 0.5 molar Solutions in Toluene

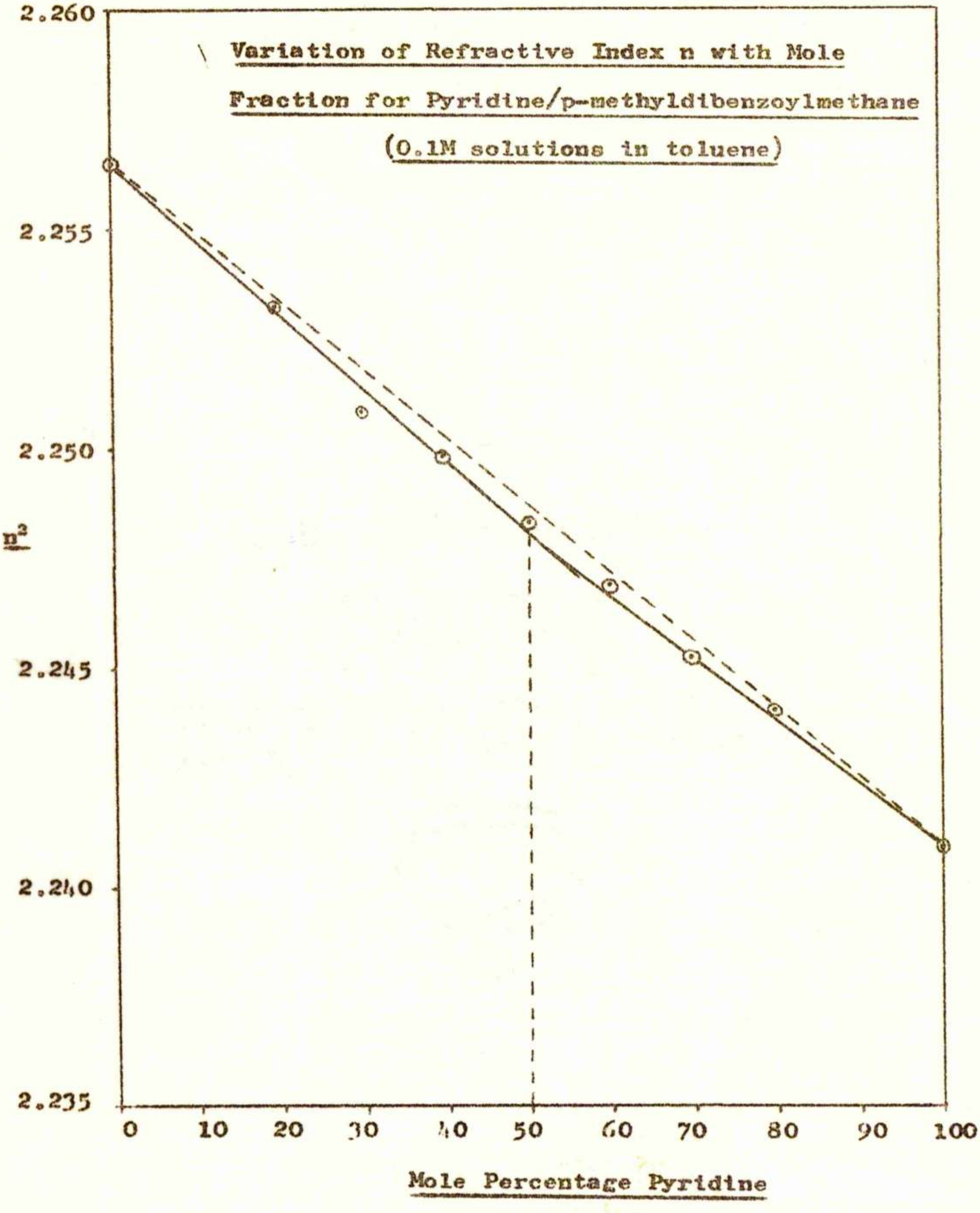
Mole % pyridine	0	20	30	40	50	60	70	80	100
n	1.5162	1.5120	1.5099	1.5078	1.5059	1.5048	1.5014	1.4992	1.4950
n^2	2.2988	2.2861	2.2798	2.2731	2.2674	2.2641	2.2541	2.4480	2.2352



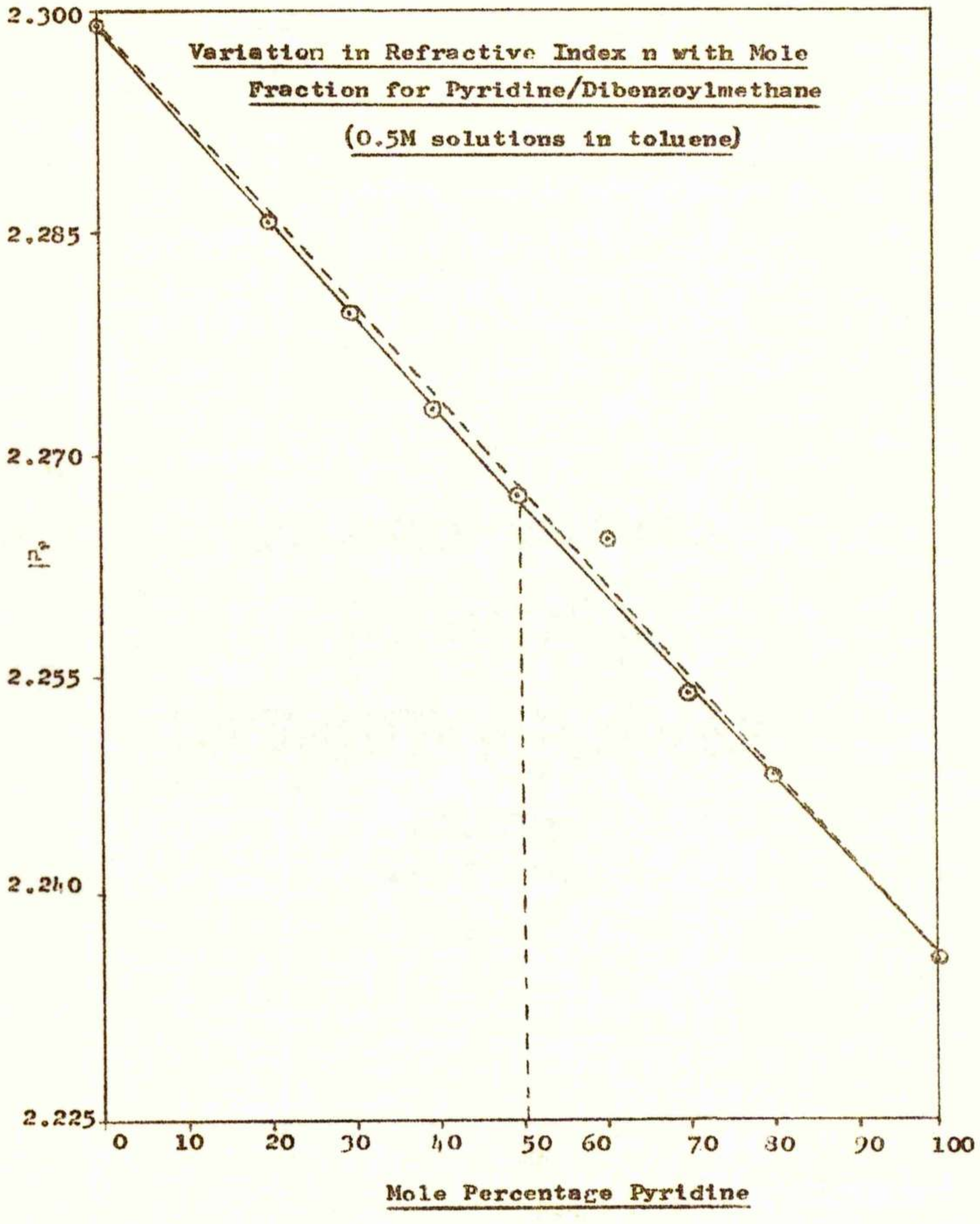
Variation of Refractive Index n with Mole Fraction for Pyridine/Acetylacetone



Variation of Refractive Index n with Mole Fraction for Pyridine/Benzoylpivaloylmethane



Variation of Refractive Index n with Mole Fraction for Pyridine/p-methyldibenzoylmethane (0.1M solutions in toluene)



Variation in Refractive Index n with Mole Fraction for Pyridine/Dibenzoylmethane (0.5M solutions in toluene)

In the cases of dibenzoylmethane and p-methyldibenzoylmethane, more concentrated toluene solutions could not be used at room temperature, since the diketones tended to crystallise out, thus destroying the accuracy required for these determinations.

Attempted Reaction of p-nitrodibenzoylmethane with Diazomethane.

To a solution of the diketone (0.4 g.) in methylene chloride (50 ml.) was added a solution of diazomethane[112] in benzene (approximately 0.7 g. of diazomethane, 10 times excess). The mixture was allowed to stand for five days, then any remaining diazomethane was destroyed by distillation into acetic acid. Crystallisation of the products gave unchanged diketone. Chromatography of the residue on alumina gave a crude oil (0.196 g.) which was not the expected ether, and could not be identified.

Preparation of the Isoxazoles.

(a) From the Diketones.

The diketone (1 mole) was dissolved in ethanol or methanol and hydroxylamine hydrochloride (ca.1.5 moles) in a little water was added. The solution was refluxed until the product separated, on cooling if necessary. The reaction time varied between 1 and 7 hr. The product was crystallised out, and purified by recrystallisation. Ultraviolet spectra were measured after each crystallisation to check whether the proportions of any mixture of products were varying. It was found that mixtures of the isoxazoles showed no appreciable change in composition after crystallisation.

(b) From the Chalcone Dibromides.

To a suspension or solution of the dibromide (1 mole) in alcohol was added hydroxylamine hydrochloride (ca. 1.5 moles) in water. The mixture was refluxed, and potassium hydroxide (3.5 moles) in water was added over a period of 15 minutes-30 min. The dibromide dissolved to form a brown solution. Reaction usually occurred within half an hour, but occasionally a lengthy period of reflux (up to 20 hr.) was required. The solution was diluted with water, acidified and extracted with methylene chloride. The products were purified by crystallisation or by chromatography on alumina.

The isomeric isoxazole pairs gave characteristic infrared and ultraviolet absorption spectra, and also, when sufficiently soluble, N.M.R. spectra.

By this second method, the following isoxazoles were obtained and characterised.

3-(p-Anisyl)-5-phenylisoxazole, from 4'-methoxychalcone dibromide, colourless plates (petroleum ether) m.p. 122-123°.

3-Phenyl-5-(p-anisyl)-isoxazole, from 4-methoxychalcone dibromide, colourless needles (petroleum ether) m.p. 126°.

3-(p-Tolyl)-5-phenylisoxazole, from 4'-methylchalcone dibromide, colourless needles (methanol), m.p. 125-126°.

3-Phenyl-5-(p-tolyl)-isoxazole, from 4-methylchalcone dibromide, colourless needles, m.p. 138-139° (methanol).

3-(p-Anisyl)-5-(p-tolyl)-isoxazole, colourless needles, m.p. 148-150° (benzene).

3-(p-Tolyl)-5-(p-anisyl)-isoxazole, colourless needles, m.p. 131-135° (benzene).

3-(p-Chlorophenyl)-5-phenylisoxazole, colourless needles, m.p. 178° (benzene). Found: C, 70.66, H, 4.14, N, 5.46, Cl, 13.36. calc. for $C_{15}H_{10}ClNO$: C, 70.47, H, 3.94, N, 5.48, Cl, 13.87%.

3-Phenyl-5-(p-chlorophenyl)-isoxazole, colourless needles, m.p. 179-180° (benzene). Found: C, 70.64, H, 4.35, N, 5.18, Cl, 13.30. calc. for $C_{15}H_{10}ClNO$. C, 70.47, H, 3.94, N, 5.48 Cl, 13.87%.

3-(p-Bromophenyl)-5-phenylisoxazole, colourless plates, m.p. 181° (benzene).

3-Phenyl-5-(p-bromophenyl)-isoxazole, colourless needles m.p. 179-180° (benzene).

3-(m-Bromophenyl)-5-phenylisoxazole, colourless needles, (petroleum ether), m.p. 119.5-122.5°. Found: C,59.65, H,3.32, N,4.67, Br,27.30. calc. for $C_{15}H_{10}BrNO$ C,60.03, H,3.36, N,4.67, Br,26.63%

3-Phenyl-5-(m-bromophenyl)-isoxazole, colourless prisms (petroleum ether), m.p. 134-135°. Found: C,60.19, H,3. N,4.78, Br,26.00, calc. for $C_{15}H_{10}BrNO$. C,60.03, H,3.36, N,4.67, Br,26.63%.

3-(β-Naphthyl)-5-phenylisoxazole, colourless prisms (benzene) m.p. 152-153°.

3-Phenyl-5-(β-naphthyl)-isoxazole, colourless needles (benzene) m.p. 167-168°.

Both nitro-chalcone dibromides gave the same isoxazole, m.p. 225°, cream needles (chloroform/methanol).

Attempts to prepare the α-naphthylisoxazoles from the dibromide gave only crude oils in which no trace of isoxazole could be detected. Similar results were obtained on attempting to prepared the isoxazoles from the chalcones via the oximes and isoxazolines.[100]

Preparation of 2,3-diphenyl-5-(α-naphthyl)-pyrazoline.[113]

Benzal-(α-acetylnaphthalene) (1.235 g.) in ethanol was treated at room temperature with phenylhydrazine (0.5 ml.) and benzyltrimethylammonium hydroxide (0.02 ml. of a 40% aqueous solution) as catalyst. On standing (19 hr.), the pyrazoline separated as yellow needles (0.462 g.). Recrystallisation (benzene/ethanol) gave yellow fluorescent needles, m.p. 176-177°.

Preparation of 2,3-diphenyl-5-(α-naphthyl)-pyrazole.[113]

The above pyrazoline (0.25 g.) was dissolved in acetone, and chromic acid (0.6 ml. of 8N solution) was added. After heating on the water bath (20 min.), excess water was added and the mixture was extracted with methylene chloride. A crude brown solid was obtained, which after chromatography on alumina (benzene/5% ether) gave a white product (0.12 g.). Recrystallis tion from benzene/ethanol gave colourless needles, m.p. 209-210°, ultraviolet $\lambda_{\text{max.}}$ 210, 225, 306 mμ (methanol).

Prolonged reaction of α-naphthoylbenzoylmethane with phenylhydrazine or the hydrochloride, under various conditions, gave no product identifiable as a pyrazole.

The structures of the isoxazoles obtained from the diket were decided by comparison, where possible, with the two isomers prepared from the chalcone dibromides. The melting points and mixed melting points were used in the assignment of structures, but the infrared and, in particular, the ultraviolet spectra were invariably used to confirm the conclusions. Where the compounds were sufficiently soluble, the N.M.R. spectra were also measured for the same purpose. Structures assigned on this basis were as follows.

p-Nitrodibenzoylmethane gave a single compound, m.p. 225°, identical with the products from the dibromides.

Known[96] to be 3-(p-nitrophenyl)-5-phenylisoxazole.

p-Methoxydibenzoylmethane[80] gave a mixture, m.p. 119-120°; an identical product was obtained when the reaction was carried out in presence of dilute sodium hydroxide. The main component was 3-(p-anisyl)-5-phenylisoxazole (NMR was used in this case).

p-Methyldibenzoylmethane[72,103,114] gave a single product m.p. 128°, identical with 3-phenyl-5-(p-tolyl)-isoxazole (confirmed by NMR). The same product was formed in presence of sodium hydroxide.

p-Methoxy-p'-methyldibenzoylmethane[72] gave a mixture, m.p. 134-135°, mainly 3-(p-anisyl)-5-(p-tolyl)-isoxazole.

p-Chlorodibenzoylmethane gave a mixture, m.p. 174-176°, mainly 3-phenyl-5-(p-chlorophenyl)-isoxazole.

p-Bromodibenzoylmethane[82] gave a mixture, m.p. 178-179°, the major component being 3-phenyl-5-(p-bromophenyl)-isoxazole.

m-Bromodibenzoylmethane gave a mixture, m.p. 123-124°, mainly 3-phenyl-5-(m-bromophenyl)-isoxazole.

α-Naphthoylbenzoylmethane gave what appeared to be a single compound, m.p. 76-77° (colourless needles, benzene petroleum ether). Found: C,84.27, H,4.93, N,5.06. calc. for $C_{19}H_{13}NO$. C,84.11, H,4.83, N,5.16%. This was thought to be 3-(α-naphthyl)-5-phenylisoxazole.

β-Naphthoylbenzoylmethane[72] gave a mixture, m.p. 158-160° the main component being 3-phenyl-5-(β-naphthyl) isoxazole.

Furoylbenzoylmethane[116] gave a product, m.p. 143-144° whose ultraviolet spectrum ($\lambda_{max.}$ 207, 243, 268 mμ, methanol) suggests the structure 3-phenyl-5-(2-furyl)-isoxazole.

Picolinylbenzoylmethane gave a single compound, m.p. 86.5-87.5°. Found: C,75.77, H,4.38, N,12.49%, calc. for $C_{14}H_{10}N_2O$: C,75.65, H,4.54, N,12.61%.

Ultraviolet Analyses of Isoxazole Mixtures.

Vierordt's method of ultraviolet analysis[48,99] was used in an attempt to determine the proportions of the isoxazole mixtures obtained from the diketones when the two isomers were available.

Ultraviolet Absorption Spectra of Diaryl-Isoxazoles

3-substituent	5-substituent	$\lambda_{max.}$ mμ and Molar Extinc^{n}. Coefficient(ε	
Phenyl	p-Anisyl	246(18,100)	284(25,000)
p-Anisyl	Phenyl		270(31,000)
p-Tolyl	p-Anisyl	250(19,700)	282(27,200)
p-Anisyl	p-Tolyl		275(32,500)
Phenyl	p-Bromophenyl	244(18,500)	274(28,200)
p-Bromophenyl	Phenyl		260(31,200)
Phenyl	m-Bromophenyl	248(20,600)	266(24,700)
m-Bromophenyl	Phenyl	247(22,500)	270(22,100)
Phenyl	p-Chlorophenyl	248(18,500)	272(26,800)
p-Chlorophenyl	Phenyl		257(27,500)

From the ultraviolet spectra of the isoxazole mixtures from the diketones, the following proportions were calculated.

p-Methoxydibenzoylmethane gave 86% 3-(p-anisyl)-5-phenylisoxazole, 14% of the 3-phenyl isomer.

p-Methoxy-p'-methyldibenzoylmethane gave 63% 3-(p-tolyl)-5-(p-anisyl)-isoxazole and 37% of the 3-(p-anisyl) compound.

p-Bromodibenzoylmethane gave 51% of 3-phenyl-5-(p-bromophenyl)isoxazole, 49% of the isomer.

m-Bromodibenzoylmethane gave 59% of the 3-phenyl compound, 41% of the 5-phenyl isomer.

p-Chlorodibenzoylmethane gave 62% of 3-phenylisoxazole and 38% of 5-phenyl compound.

Test Mixtures

(A) A mixture of the p-methoxy compounds, containing 78.5% of 3-(p-anisyl)-5-phenylisoxazole, gave, on analysis, a calculated content of 83.2%.

(b) A mixture of the p-methoxy-p'-methyl isoxazoles, containing 37.8% of 3-(p-anisyl)-5-(p-tolyl)-isoxazole, gave a result of 26.0% of this compound.

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