THESIS

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STUDIES IN THE PYRAZOLIDINE AND METAL CHELATE FIELDS.

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

The author wishes to express his appreciation to Dr. G. T. Newbold and Professor F. S. Spring for their guidance and council during the compiling of Part I of this study, and to Dr. D. C. Nonhebel and Professor P. L. Pauson for their continued interest and advice during the preparation of Part II.

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PART I

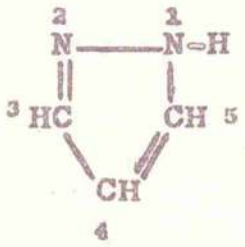
STUDIES IN THE PYRAZOLIDINE FIELD

INTRODUCTION

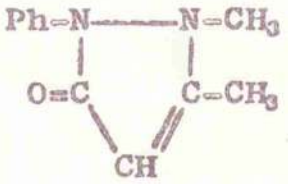
PART I.

The pyrazole ring system (I) consists of a doubly unsaturated five-membered ring containing two adjacent nitrogen atoms. The pioneering work on this ring system was carried out by L. Knorr (1883),[1,2] and subsequent work has led to the discovery of antipyrine[3] (II), related compounds, and phenylbutazone[4] (III), clinically important drugs. It is not definitely known whether or not this ring system occurs naturally, and all the members are obtained by synthesis.

The chemistry of pyrazole and its derivatives is discussed by Jacobs in "Heterocyclic Compounds",[5] the nomenclature of the system is shown (I), numbering commencing at the acidic nitrogen.



(I)



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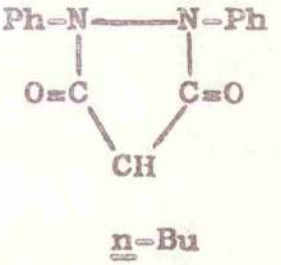
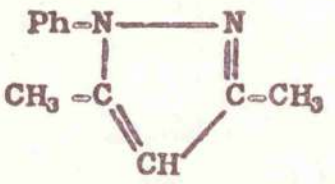


(III)

Pyrazoles can be prepared by three general methods;

(a) reaction of hydrazine or its derivatives with 1,3-dicarbonyl compounds,[5]

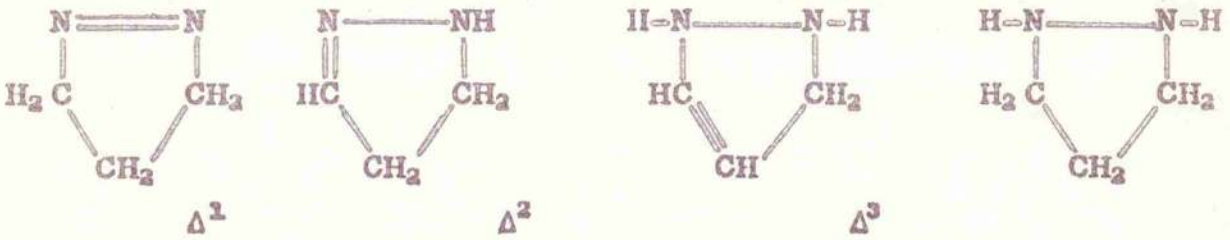
e.g. $CH_3COCH_2COCH_3$ + $PhNH.NH_2$ ⟶



(b) reaction of hydrazine with αβ-unsaturated carbonyl compounds.[7]

(c) reaction of aliphatic diazo compounds such as diazomethane or diazoacetic ester, with acetylenes or olefines.[8]

Formal reduction of the pyrazole ring gives first dihydropyrazoles (pyrazolines) (IV) and then tetrahydro pyrazoles (pyrazolidines) (V).



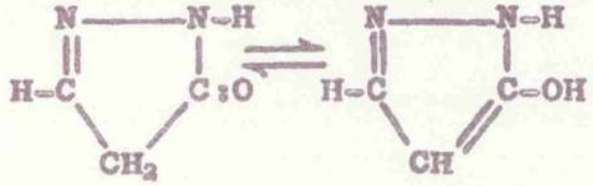
Δ^1 Δ^2 Δ^3

(IV) (V)

The three isomeric pyrazolines are indicated, the Δ^2 being the most stable form. However, these relatively unstable compounds are not prepared by reduction of the pyrazoles,

but by ring closure methods similar to those used for the pyrazoles.[9,10,11] The main interest in the pyrazolidines lies in the 3,5-dioxo-derivatives, which will be discussed later.

Other important derivatives of the pyrazole system are the hydroxypyrazoles, (pyrazolones, oxopyrazolines) (VI).



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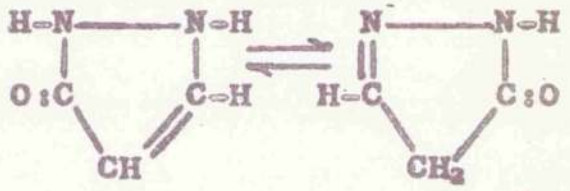


3- 5-

(VII)

These compounds exist as keto-enol tautomers (VI) with tautomerism also occurring between the two keto forms (VII). However, with substitution on the NH function, these keto tautomeric forms are 'frozen' to form the 3-oxopyrazoline and 5-oxopyrazoline series.

The main method of synthesis of these oxopyrazolines involves the reactions of β-aldehydo, β-keto esters, and acyl malonic esters with mono- and di-substituted hydrazines.[12]

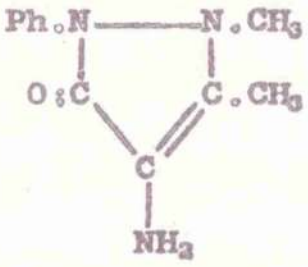
(VIII)

The important series, the 5-oxopyrazolines, has been more thoroughly investigated than any other pyrazole series, in

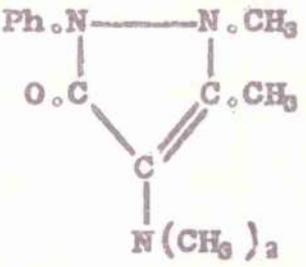
connection with dye manufacture,[13,14] and more relevantly with the production of antipyretic drugs, stimulated by the discovery of antipyrine (II).

Antipyrine,[3] (2,3-dimethyl-5-oxo-1-phenylpyrazoline) is prepared from 3-methyl-5-oxo-1-phenylpyrazoline (VIII) by methylation with methyl iodide in methanol at 100°,[15] or industrially by methylation with methyl chloride under high pressure.[16] The drug receives its name for its antipyretic and analgesic properties, which are shared by several of its derivatives, and these have been adopted for widespread medicinal use.

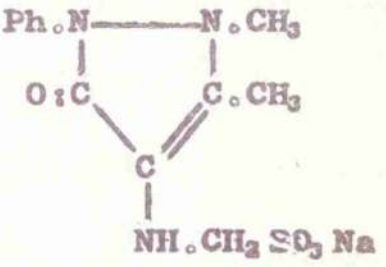
The main derivatives are aminoantipyrine (IX), pyramidone (X), and melubrin (XI). The first of these



(IX)

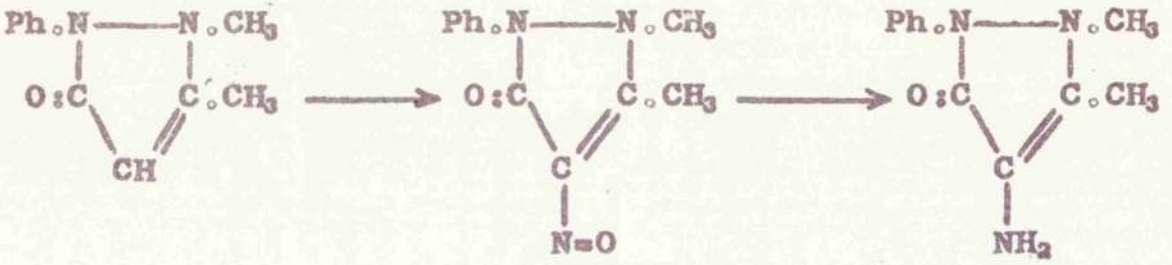


(X)



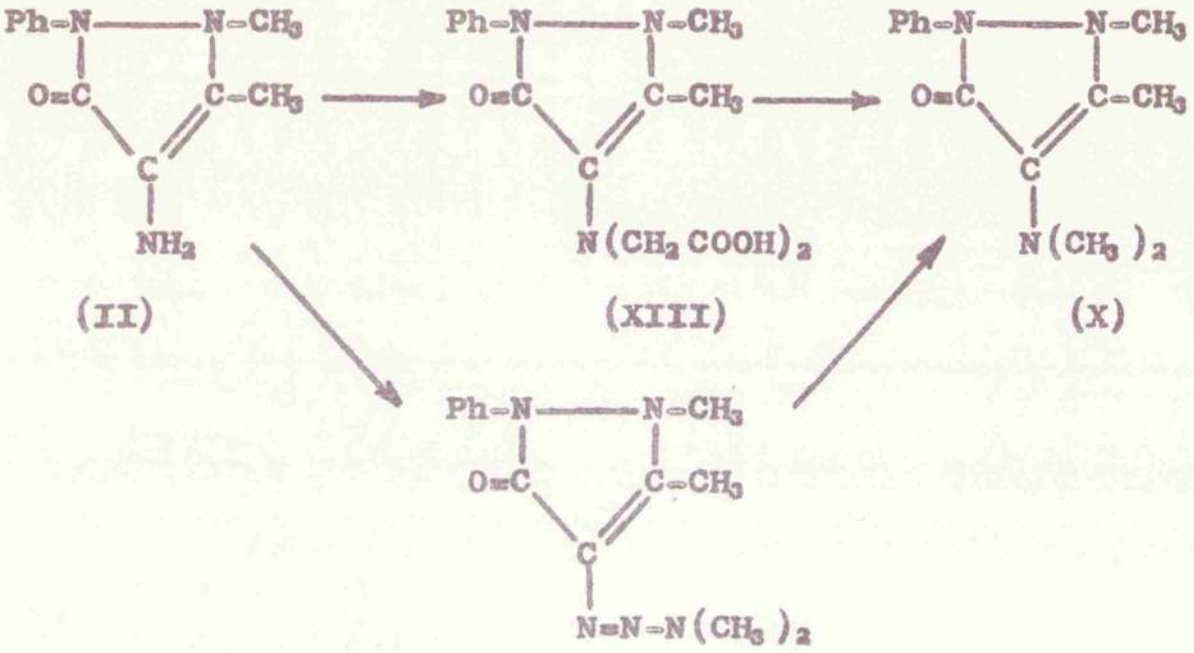
(XI)

is prepared by nitrosation of antipyrine, giving the 4-nitrosoantipyrine (XII), followed by reduction of this with zinc dust and acetic acid.



(II) (XII) (IX)

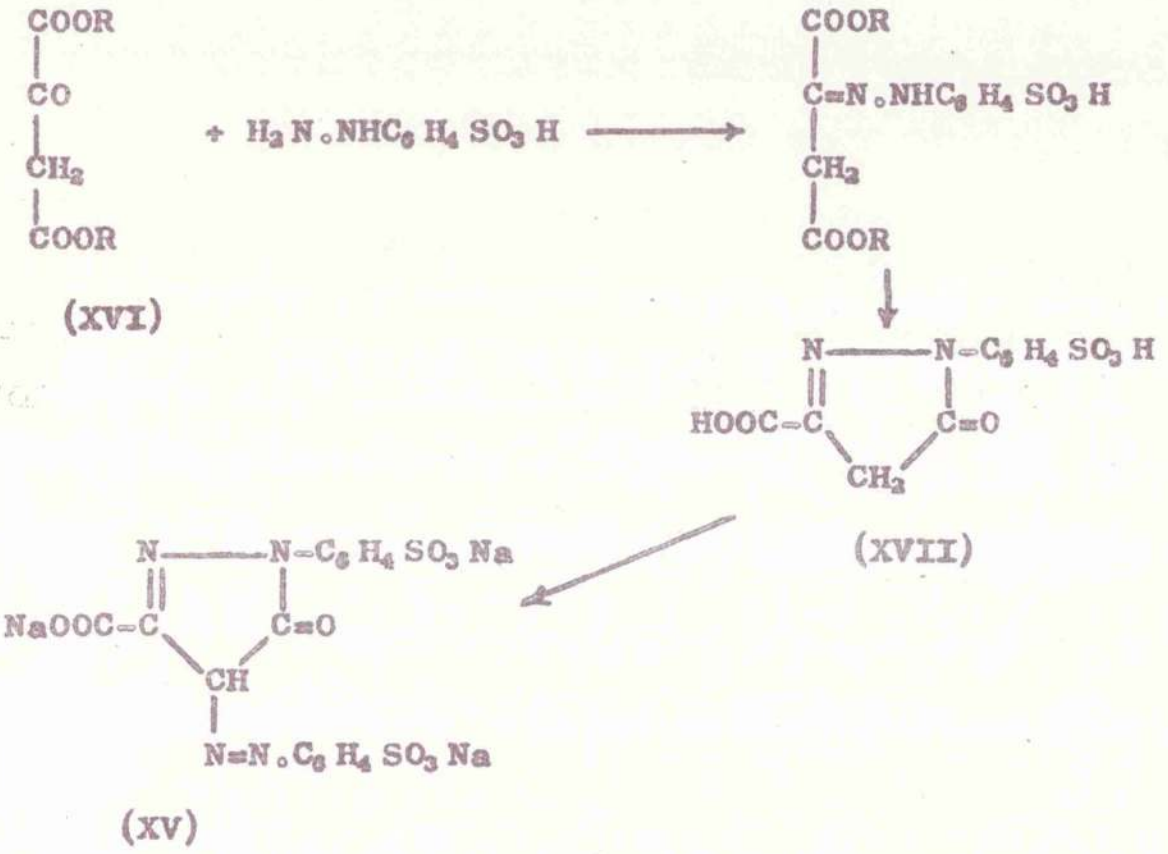
Pyramidone (X), prepared by methylation of aminoantipyrine,[17] is a more powerful antipyretic and is less toxic than antipyrine itself. Various methods of conversion of aminoantipyrine into pyramidone are employed, including the reaction of aminoantipyrine with chloracetic acid[18] giving initially the carboxylic acid (XIII) which is decarboxylated to give pyramidone. The diazotisation of aminoantipyrine with nitroso-dimethylamine[19] gives the intermediate (XIV) which then loses nitrogen to form pyramidone. Commercially the drug is obtained by treating 4-nitrosoantipyrine (XII) with an excess of sodium bisulphite.[20] The resultant 4-sulphamino-antipyrine is then methylated by treatment with formaldehyde and formic acid, giving pyramidone.



However, recent discoveries[21,22] that antipyrine can cause severe and even fatal agranulocytoic angina have led to the total abandonment of the drug in Britain and North America, although it still enjoys widespread use on the European continent. Pyramidone has also lost favour with the introduction of the less toxic salicylates.

As well as having useful medicinal properties however, as mentioned previously, the pyrazolones and their derivatives include many important commercial dyes. These dyes are very fast to light, and are particularly valuable as the yellow components in two and three colour mixtures for dyeing wool. Tartrazine[24] (XV), the first pyrazolone dye used, still

enjoys considerable importance both as a yellow wool dye, and especially as a synthetic colourant for foodstuffs. It is obtained commercially by condensation of oxalacetic ester (XVI) with phenylhydrazine sulphonic acid. The resultant sulphophenylpyrazolone carboxylic acid (XVII) is then coupled with diazotised sulphanilic acid giving tartrazine.



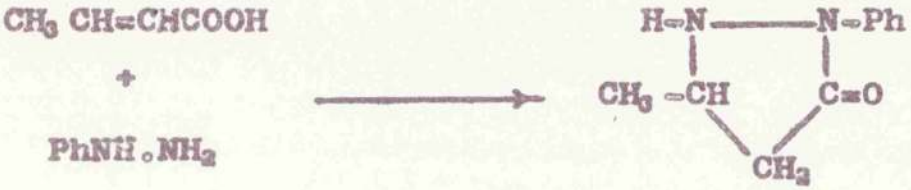
(XVI)

(XVII)

(XV)

Further derivatives of the pyrazole system, the oxopyrazolidines are prepared by analogous methods to those used for the above. Heating unsaturated acids with hydrazines is the main method of synthesis; crotonic acid

with phenylhydrazine giving 3-methyl-5-oxo-1-phenylpyrazolidine (XVIII).[23]



(XVIII)

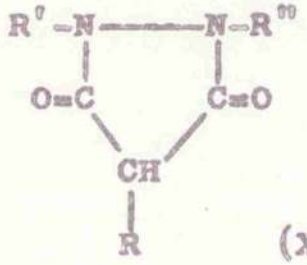
However, these compounds are relatively unimportant.

Finally, and most relevantly, derivatives of pyrazole with two oxygen functions, the main series being the 3,5-dioxopyrazolidines, will be discussed. These compounds can be prepared by several general synthetic methods, especially by heating malonic esters with hydrazines in the presence of sodium ethoxide,[24,25] or

by reaction of malonyl chlorides alone with hydrazines, especially hydrazobenzene.[24,26]

The stimulus for the investigation of derivatives of the 3,5-dioxopyrazolidines, was the discovery that 1,2-di-aryl-3,5-dioxopyrazolidines, and in particular 4-n-butyl-3,5-dioxo-1,2-diphenylpyrazolidine, (phenylbutazone) (III), possess interesting and important pharmacological

properties. However, it was found that although phenylbutazone is of value clinically in the treatment of rheumatoid arthritis, and allied conditions, several indications of the toxic effects associated with its use have been reported.[27-30] Hence many allied compounds of general formula (XIX) have been synthesised, in an attempt to obtain a drug with the pharmacological effect of phenylbutazone, but without its attendant toxicity.

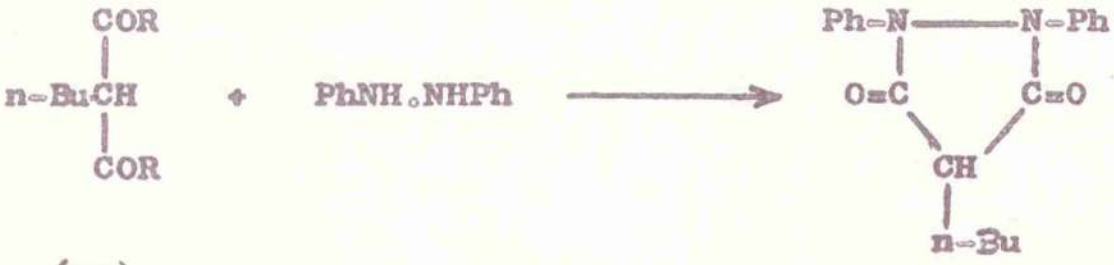


R is alkyl, aralkyl or aryl.

R^{I}, R^{III} - usually aryl, or benzyl.

(XIX)

Phenylbutazone itself can be prepared by the general methods of synthesis of 3,5-dioxopyrazolidines, either by condensation of ethyl n-butylmalonate (XX, R=OEt), or n-butylmalonyl chloride (XX, R=Cl) with hydrazobenzene.

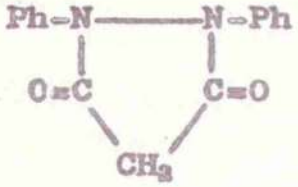


(XX)

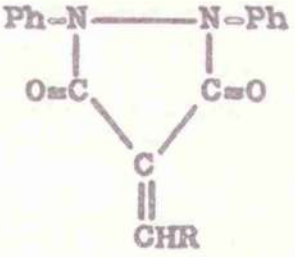
Many other methods of synthesis of this compound have been patented.[31,32,33]

It was felt that due to the lack of comprehensive reviews on the 3,5-dioxopyrazolidines, a brief summary of the chemistry of these compounds, most relevant to the work described, was necessary at this stage.

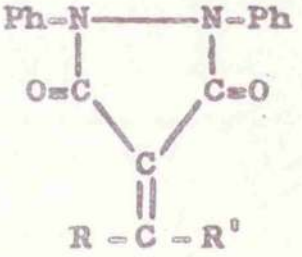
3,5-Dioxo-1,2-diphenylpyrazolidine (XXI) can be prepared by any of the above general methods. The 4-position in this compound acts as an active methylene group, condensing readily with aldehydes and ketones to form compounds of type (XXII) and (XIII) respectively.



(XXI)



(XXII)



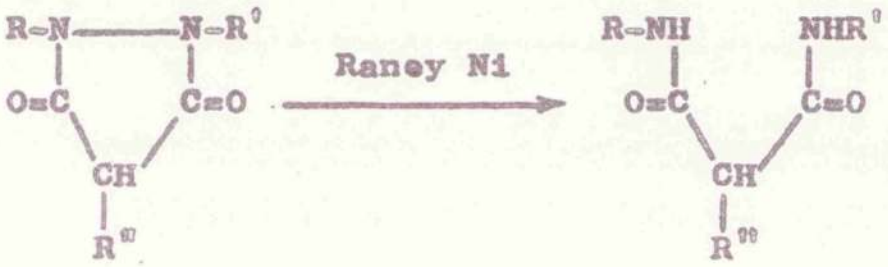
(XXIII)

Tsumaki has prepared a large number of these highly coloured derivatives.[34,35]

3,5-Dioxo-1,2-diphenylpyrazolidine (XXI) reacts with nitrous acid to give the 4-isonitroso derivative (XXIV), which can be reduced catalytically to 4-amino-3,5-dioxo-1,2-diphenylpyrazolidine (XXV).[36]

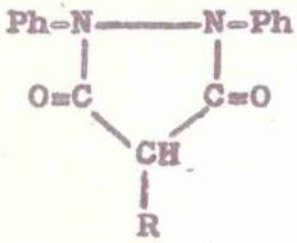
(XXIV) (XXV)

Treatment of 3,5-dioxo-1,2-diphenylpyrazolidine or any of its 4-substituted derivatives with Raney nickel at temperatures above room temperature, results in cleavage of the pyrazolidine ring between the nitrogen atoms, giving substituted malondianilides[37] (XXVI).

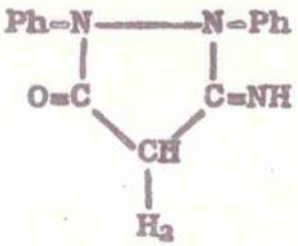


(XXVI)

Owing to the clinical value of phenylbutazone (XXVII, R = *n*-Bu) extensive investigations have been carried out on derivatives of 3,5-dioxo-1,2-diphenylpyrazolidine (XXVII, R = H) substituted in the 4-position,[34,35,36,38,39] or in the phenyl rings,[26] or both.[38,40] However, recent synthesis of a compound with one of the oxo groups replaced by an imino group,[41] 3-imino-5-oxo-1,2-diphenylpyrazolidine (XXVIII), led to the possibility of a parallel series of compounds, which could also have clinical significance.

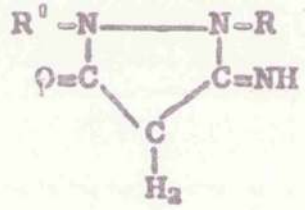


(XXVII)



(XXVIII)

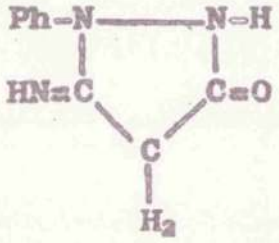
Some 1-alkyl-2-aryl-3(5)-imino-5(3)-oxopyrazolidines (XXIX, R = alkyl, R^0 =alkyl or aryl) have been reported,[42,43] and they have antipyretic properties. These compounds can be synthesised by alkylation of the corresponding 1-aryl-3(5)-imino-5(3)-oxopyrazolidines (XXIX, R=H, R^0 = aryl); for example methylation of 3-imino-5-oxo-1-phenylpyrazolidine (XXIX, R = H, R^0= phenyl) gives 2-methyl-3-imino-5-oxo-1-phenyl pyrazolidine (XXIX, R= Me, R^0=PH).[44]



(XXIX)

Several methods of synthesis of the imino-oxo series are available. One of these involves the condensation of phenylhydrazine with ethyl cyanoacetate under base catalysed conditions, giving what was at first thought to be 5-imino-3-oxo-1-phenylpyrazolidine[45] (XXX). It was later proved that the actual compound formed, was the isomeric 3-imino-5-oxo-1-phenylpyrazolidine (XXIX, R=H, R^0=phenyl).[30,46] However, the above reaction is not general. For example 2-pyridylhydrazine, and 2-quinolylhydrazine with ethyl cyanoacetate give the respective 5-imino-3-oxo-pyrazolidines.[47] These hydrazines can also be condensed with ethyl malonate monoimidoester (XXXII),[48] to form the isomeric 3-imino-5-oxo-pyrazolidines (XXXI).

In this way, the required pyrazolidine is obtained via the intermediate ethyl β-(β-substituted-hydrazine)-β-iminopropionate, (XXXIII), the latter being ring closed by alkali.



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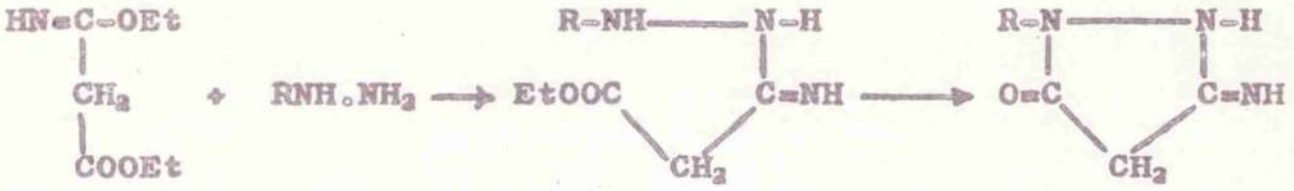


(XXXII) (XXXIII) (XXXI)

The general synthesis of the 5-imino-3-oxo-1-aryl pyrazolidines is the condensation of cyanoacetyl chloride, or azide (XXXIV), with a hydrazine.[49]

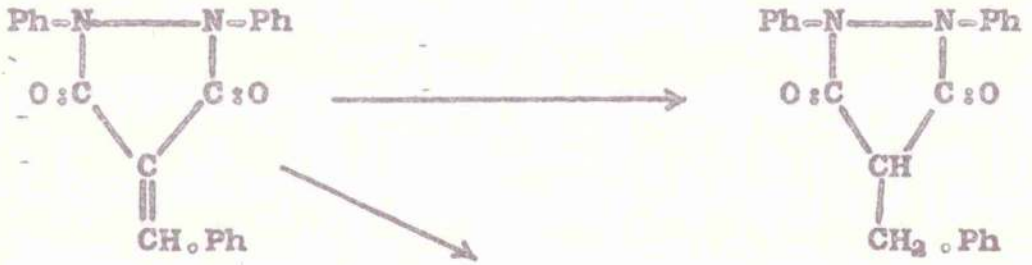
(XXXIV)

The main object of this work was to synthesise, and examine both from a chemical and physiological aspect, substituted derivatives of 3-imino-5-oxo-1,2-diphenylpyrazolidine (XXVIII). In these compounds, the 3- and 5-positions are equivalent, and the problem of isomerism does not occur.

THEORETICAL

PART I

The initial work involved an investigation into the products formed by the action of Raney nickel on 4-benzylidene--3,5-dioxo-1,2-diphenylpyrazolidine[34] (XXXV), this being one of the methods of preparation of the 4-benzyl derivative.[40] Subsequently, it was found that on refluxing 4-benzylidene-3,5-dioxo-1,2-diphenylpyrazolidine (XXXV) with Raney nickel, 4-benzyl-3,5-dioxo-1,2-diphenylpyrazolidine (XXXVI), and C-benzylmalonodianilide (XXXVII) were produced, the latter being by far the main product. This latter compound was identified by comparison of its infrared and ultraviolet spectra with those of other substituted malonodianilides. A precedent for this type of ring opening has already been mentioned.[37]



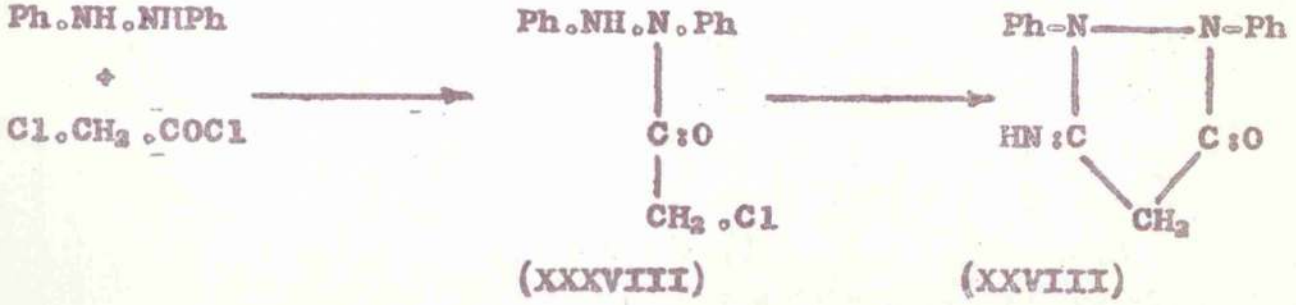
$PhCH_2.CH.(CONHPh)_2$

(XXXV) (XXXVII) (XXXVI)

The first object of the work involving the 3-imino-5--oxopyrazolidines was the preparation of 3-imino-5-oxo-1,2-diphenylpyrazolidine (XXVIII). Previous reports on this compound indicated that it could not be prepared by the

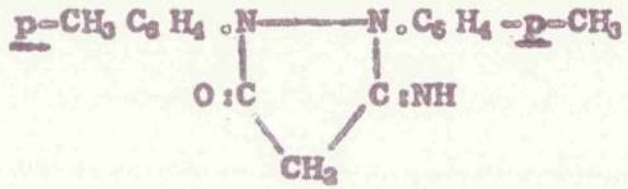
condensation of ethyl cyanoacetate with hydrazobenzene.[53] However, the condensation was attempted using prolonged reflux conditions, with sodium ethoxide as the basic catalyst, and in this way 3-imino-5-oxo-1,2-diphenylpyrazolidine was obtained in low yield, (10%). In an attempt to find alternative methods of synthesis, hydrazobenzene was refluxed with cyanoacetoamide in presence of molar quantities of sodium ethoxide, but no trace of 3-imino-5-oxo-1,2-diphenylpyrazolidine was obtained, even after prolonged refluxing.

The initial synthesis of 3-imino-5-oxo-1,2-diphenyl pyrazolidine involved the condensation of hydrazobenzene with cyanoacetyl chloride, the intermediate cyanoacetylhydrazobenzene cyclising under the reaction conditions.[41] However, the preparation of pure cyanoacetyl chloride was difficult in that the reaction of cyanoacetic acid and thionyl chloride tended to give charred residues, and hence a variation of this method was developed. Condensation of hydrazobenzene with chloroacetyl chloride yielded chloroacetylhydrazobenzene (XXXVIII), in almost theoretical yield. This material on treatment with an aqueous ethanolic solution of potassium cyanide, gave 3-imino-5-oxo-1,2-diphenylpyrazolidine in 30% yield.



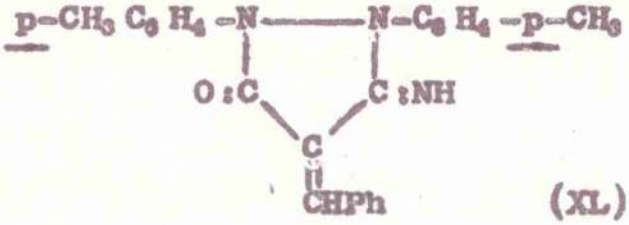
(XXXVIII) (XXVIII)

3-Imino-5-oxo-1,2-di-p-tolylpyrazolidine (XXXIX) was synthesised by condensation of ethyl cyanoacetate with 4,4'-dimethylhydrazobenzene. Once again the yield was poor, (8%).



(XXXIX)

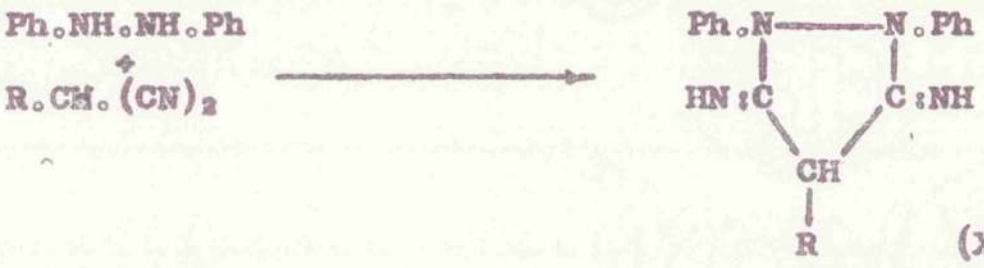
Condensation of this compound with benzaldehyde gave 4-benzylidene-3-imino-5-oxo-1,2-di-p-tolylpyrazolidine (XL) in poor yield. This reaction helped to confirm, that in contrast to the 3,5-dioxopyrazolidines, the imino-oxo-pyrazolidines condense far less readily with aldehydes and ketones. 4-Benzylidene-3,5-dioxo-1,2-diphenylpyrazolidine (XXXV) by contrast is prepared in good yield simply by heating 3,5-dioxo-1,2-diphenylpyrazolidine with benzaldehyde, and cooling the reaction mixture.[34] Parallel work[51] on the condensation of 3-imino-5-oxo-1,2-diphenylpyrazolidine with a variety of aldehydes and ketones, agrees with the above conclusion.



(XL)

Having synthesised compounds with one oxo group replaced by an imino group, interest was aroused as to the

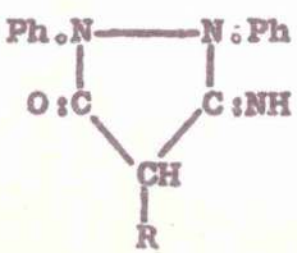
possibility of the formation of a series of compounds with both oxo groups replaced by imino (XLI) by condensation of substituted malononitriles with hydrazobenzene.



(XLI)

However, even after prolonged refluxing of malononitrile and hydrazobenzene in ethanol, with molar quantities of sodium ethoxide, no 3,5-di-imino-1,2-diphenylpyrazolidine, (XLI, R = H) could be isolated, the starting materials being recovered.

Having synthesised 3-imino-5-oxo-1,2-diphenylpyrazolidine (XXVIII), and 3-imino-5-oxo-1,2-di-p-tolylpyrazolidine (XXXIX), the above methods of synthesis were extended, in an attempt to obtain 4-alkyl derivatives. Owing to the close similarity in structure, if not in chemical activity, between the dioxopyrazolidines and the imino-oxopyrazolidines, the initial interest lay in the synthesis of 4-n-butyl-3-imino-5-oxo-1,2-diphenylpyrazolidine (XLII, R = n-Bu) (cf. phenylbutazone (I, R = n-Bu).

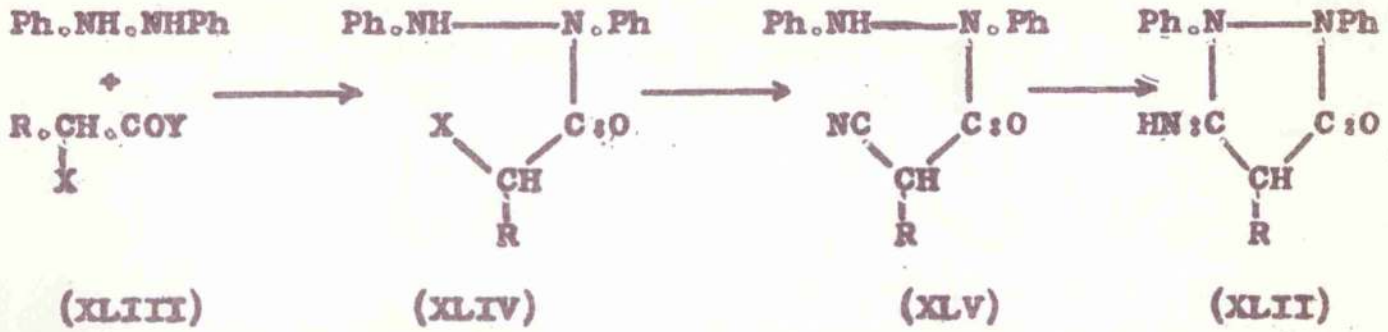


(XLII)

A base catalysed condensation of ethyl n-butylcyanoacetate and hydrazobenzene failed to give the above compound. Since the yields of the previous ester condensations were poor, this result was not unexpected, and the other methods of synthesis were used.

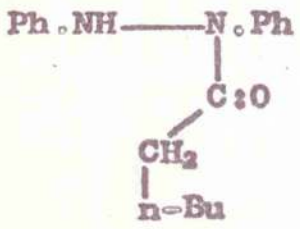
n-Butylcyanoacetyl chloride (XLIII, R = n-Bu, X = CN) was prepared by the action of thionyl chloride on the acid. Because of the great instability of cyanoacyl chlorides no attempt was made to distil the product. However, the formation of the acyl chloride was confirmed by formation and identification of the amide. Condensation of equimolar quantities of the acyl chloride with hydrazobenzene, in chloroform/pyridine, gave benzidine as the sole crystalline product. Variations in the molar proportions also failed to give any trace of the required pyrazolidine.

Because of the difficulty of isolating reasonable quantities of pure α- substituted cyanoacetyl chlorides, the variation of this method of synthesis using the α-haloacyl halides was next investigated.

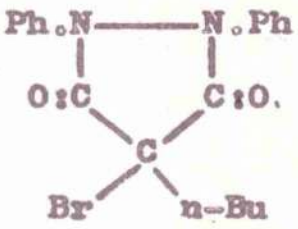


(XLIII) (XLIV) (XLV) (XLII)

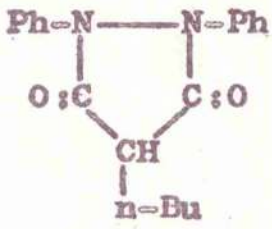
Condensation of bromocaproyl bromide (XLIII, R = n-Bu, X, Y= Br) with hydrazobenzene in chloroform/pyridine gave a viscous red gum, which, after extensive treatment with solvents, failed to give any solid except azobenzene, formed by oxidation of the hydrazobenzene. It was assumed that initial formation of α-bromocaproylhydrazobenzene had occurred, (XLIV, R = n-Bu, X = Br) and the gum was refluxed with an aqueous ethanolic solution of potassium cyanide. Caproylhydrazobenzene (XLVI) was obtained, formed by reductive dehalogenation of the intermediate α-bromocaproyl-hydrazobenzene, (XLIV R = n-Bu, X = Br) either by the excess hydrazobenzene present, or by the cyanide ion, with formation of cyanogen bromide in the latter case. A precedent, for this reductive dehalogenation involving hydrazobenzene, had been noticed during the preparation of 4-bromo-4-n-butyl-3,5-dioxo-1,2-diphenylpyrazolidine (XLVII) by the condensation of n-butyl-bromomalonic ester with hydrazobenzene. In addition to the desired product, 4-n-butyl-3,5-dioxo-1,2-diphenylpyrazolidine (III) was also isolated.



(XLVI)



(XLVII)



(III)

However, although this would indicate that the dehalogenation was caused by hydrazobenzene, it is noted that caproylhydrazobenzene was only isolated after the treatment with potassium cyanide solution, and this was found to be the case in all subsequent dehalogenations. No dehalogenation occurred, as will be seen later, if the intermediate haloacylhydrazobenzene was isolated and purified before treatment with potassium cyanide, and this seems further evidence that the reduction is due to hydrazobenzene under the basic conditions produced by the cyanide ion.

Repetition of the condensation of α-bromocaproyl bromide with hydrazobenzene, using a large excess of the acyl bromide to minimise dehalogenation, gave a trace of solid, m.p. 160° which, having no carbonyl frequency in the infrared spectrum, was not the required acylhydrazobenzene, and was not investigated further. No other solid was isolated.

The condensation was repeated in chloroform-dimethylaniline, the method being instigated by absence of dehalogenation when the method of synthesis of 4-bromo-4-n-butyl-3,5-dioxo-1,2-diphenylpyrazolidine was carried out in the above solvents. A viscous red gum was obtained from which azobenzene was isolated as the sole crystalline product.

Subsequent treatment of the gum with potassium cyanide in aqueous ethanol gave caproylhydrazobenzene.

A further condensation was carried out with addition of the hydrazobenzene to the acyl bromide, in an attempt to eliminate dehalogenation. A red gum was again obtained from which no solid other than azobenzene could be isolated. Treatment of this with potassium cyanide gave a further red gum, which gave a red colour with ferric chloride solution. Chromatography of the gum on alumina gave traces of caproylhydrazobenzene (XLVI), and although several fractions gave a red colour with ferric chloride solution, no other solid was isolated. Repetition of this condensation on a larger scale produced the same products.

The final condensation of α-bromocaproyl bromide with hydrazobenzene was carried out in ether according to Bischoff.[55] A red gum was once again obtained from the initial reaction, and this on subsequent treatment with potassium cyanide gave azobenzene as the sole crystalline product.

Owing to the failure of the bromoacyl bromide to give satisfactory condensation, the condensation was attempted using α-bromocaproyl chloride (XLIII, R=n-Bu, X=Br, Y = Cl). Condensation of this with hydrazobenzene again

produced a red oil from which no solid could be isolated. Treatment of the oil with potassium cyanide in aqueous ethanol gave azobenzene, and caproylhydrazobenzene as the only crystalline products.

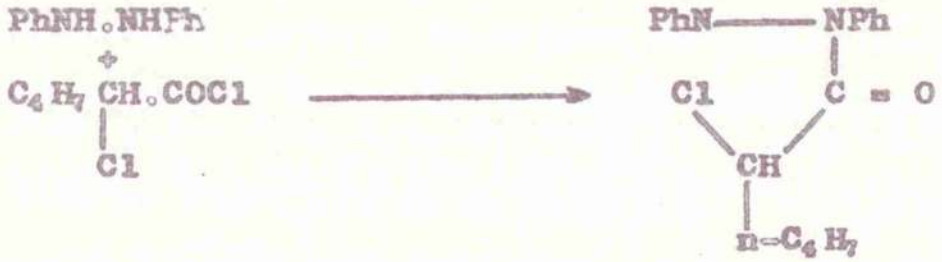
Condensation of α-bromocaproyl chloride with hydrazobenzene in ether gave a red oil from which no solid other than azobenzene could be obtained.

A further series of condensation was attempted using α-chlorocaproyl chloride and hydrazobenzene. General methods of synthesis of chloroacyl chlorides were used in an attempt to prepare the chlorocaproyl chloride, there being no reference to this compound in the literature. Treatment of caproyl chloride with sulphuryl chloride, in presence of iodine as a promoter, failed to give substitution. Caproic acid was then reacted with chlorine, in presence of a trace of phosphorus trichloride, in an attempt to prepare chlorocaproic acid.[53] Only a trace of the required product was isolated.

The above synthesis was adapted, by using a large excess of phosphorus trichloride to ensure initial formation of caproyl chloride. Fractional distillation of the reaction mixture yielded an acid chloride, b.p. 174° (caproyl chloride b.p. 153°), which formed a monochlorocaproylamide. From a comparison of boiling points of

α- and β-chloroacyl chlorides it was apparent that the chlorine was in the α-position.

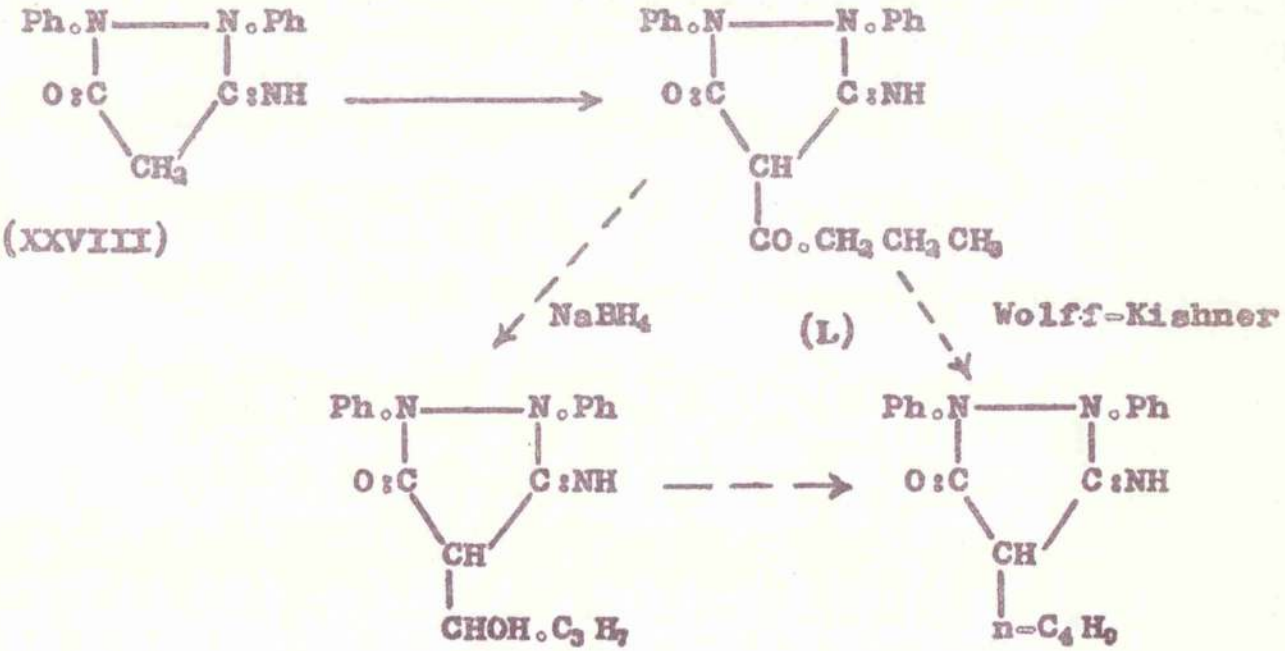
Condensation of α-chlorocaproyl chloride (XLVIII) with hydrazobenzene gave eventually N-α-chlorocaproyl hydrazobenzene (XLIX) in good yield as white plates. However, attempted cyclisation of this intermediate with potassium cyanide in aqueous ethanol failed, even on variation of the molar quantities and the experimental conditions, in that no solid other than azobenzene could be isolated. No caproylhydrazobenzene was isolated.



(XLVIII) (XLIX)

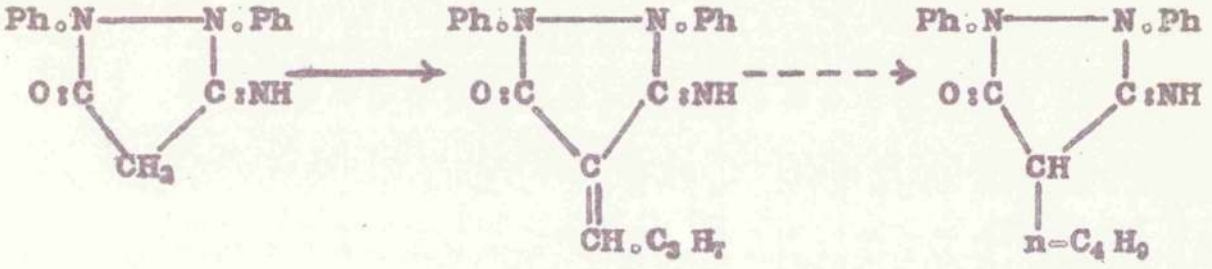
In an attempt to replace the α-chlorine atom by nitrile, other metal cyanides were used. Treatment of N-α-chlorocaproylhydrazobenzene (XLIX) with copper cyanide in aqueous ethanol failed to effect replacement, the starting material being recovered. Similarly, the N-α-chlorocaproylhydrazobenzene was recovered unchanged after refluxing with silver cyanide in toluene.[54] Further, N-α-chlorocaproylhydrazobenzene was recovered unchanged after standing for 24 hr. in liquid hydrogen cyanide.

Because of the lack of success in synthesising 4-n-butyl-3-imino-5-oxo-1,2-diphenylpyrazolidine, by cyclisation methods, attempts were made to prepare this compound through 3-imino-5-oxo-1,2-diphenylpyrazolidine. The initial method of preparation attempted, involved the formation of 4-butyroyl-3-imino-5-oxo-1,2-diphenylpyrazolidine (L) with subsequent reduction of the side-chain carbonyl group to $-CH_2$. Condensation of butyroyl chloride with 3-imino-5-oxo-1,2-diphenylpyrazolidine gave the required 4-butyroyl derivative, (L), but yields were negligible, and the synthesis was carried no further.



The second method of synthesis attempted involved the reduction of 4-butylidene-3-imino-5-oxo-1,2-diphenylpyrazolidine (LI), formed by condensation of butyraldehyde with

3-imino-5-oxo-1,2-diphenylpyrazolidine.

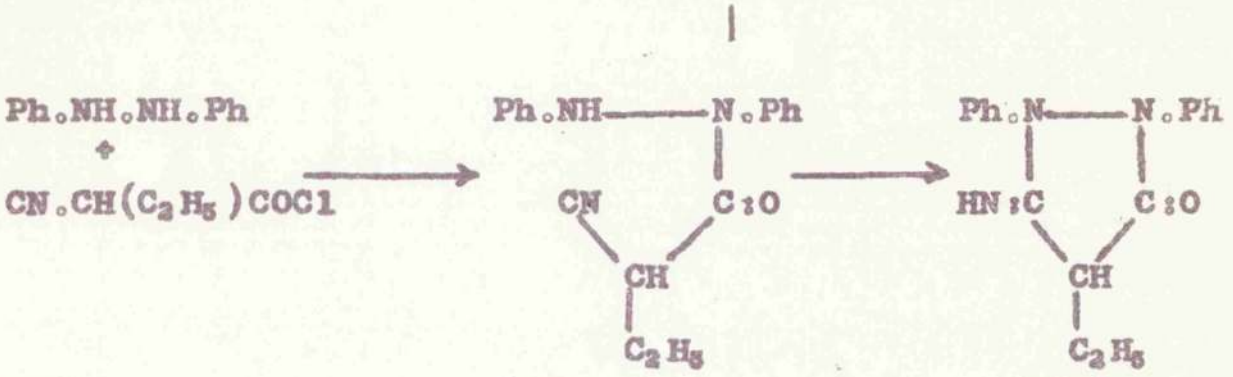


(LI)

Parallel work showed that this compound could not be reduced by catalytic methods,[51] and an attempted chemical reduction using zinc metal in concentrated hydrochloric acid, also failed to convert the 4-butylidene derivative to the 4-butyl homologue, the starting material being recovered.

Owing to the failure to prepare 4-n-butyl-3-imino-5-oxo-1,2-diphenylpyrazolidine, it was decided that the synthesis of 4-ethyl-3-imino-5-oxo-1,2-diphenylpyrazolidine (LII), should be attempted, to investigate the limits of the above synthetic methods in preparing 4-alkyl pyrazolidines, the 4-methyl homologue having already been synthesised.[41]

Condensation of ethylcyanoacetyl chloride (LIII) with hydrazobenzene gave a trace of white solid, m.p. 104° which showed both carbonyl and nitrile frequencies in the infrared spectrum. Analysis confirmed that it was the intermediate N-α-cyanobutyroylhydrazobenzene (LIV). Attempted cyclisation of this compound with molar sodium carbonate solution failed, the starting material being recovered.

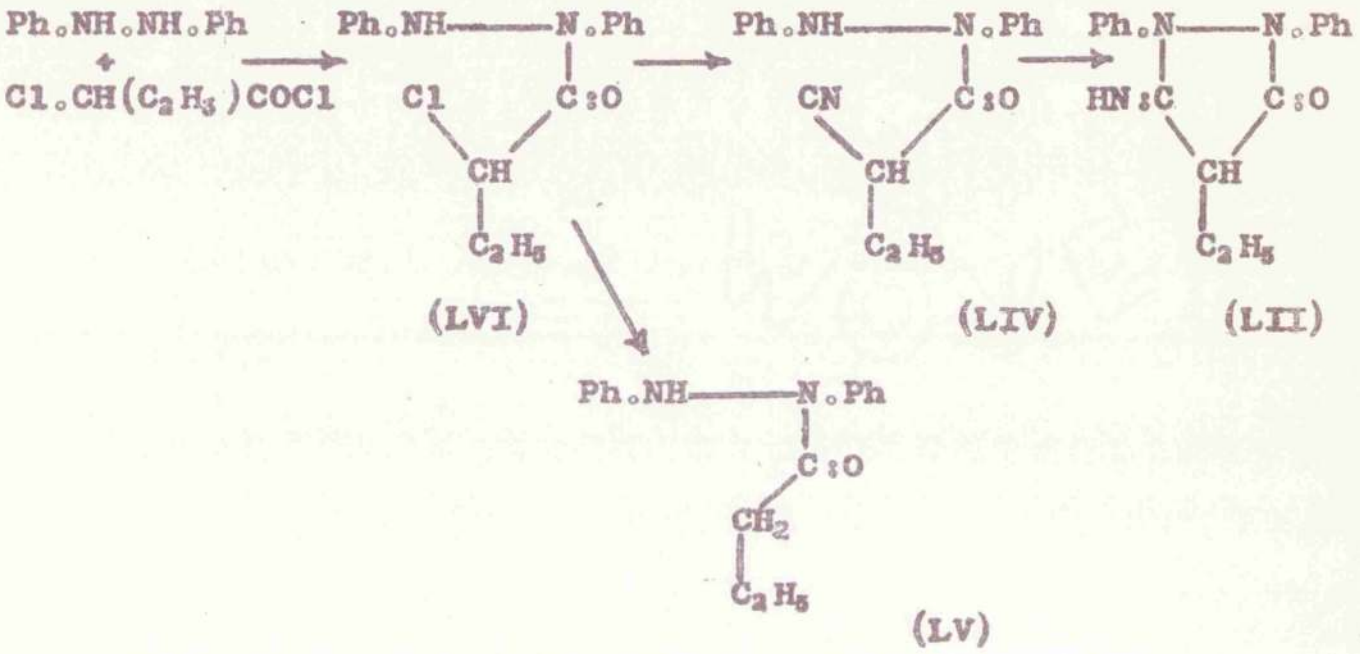


(LIII) (LIV) (LII)

Repetition of the above condensation using a 3:1 molar ratio of acyl chloride to hydrazobenzene gave eventually a red viscous gum, from which no solid other than azobenzene could be isolated, even on seeding the mother liquors with N-α-cyanobutyroylhydrazobenzene. The mother liquors did however give a red colour with ferric chloride solution.

The adaptation of this method using α-chlorobutyroyl chloride was next attempted. Condensation of this reagent with hydrazobenzene gave an intractable red gum, which on treatment with a solution of potassium cyanide in aqueous ethanol yielded two crystalline products. The first of these, m.p. 120° was identified as N-butyroylhydrazobenzene (LV) formed by reductive dehalogenation of the intermediate α-chloro derivative. The second compound m.p. 206°, had infrared and ultraviolet spectra very similar to those of 3-imino-5-oxo-1,2-diphenylpyrazolidine (XXVIII), and 4-methyl-3-imino-5-oxo-1,2-diphenylpyrazolidine (XLII, R = Me),[41] and also gave a red colour with ferric chloride solution. Analysis confirmed that it was the required

4-ethyl-3-imino-5-oxo-1,2-diphenylpyrazolidine (LII) (0.5%).



Careful repetition of the above condensation with very slow addition of the acyl chloride gave α-chlorobutyroyl-hydrazobenzene (LVI) in 50% yield. Treatment of this with potassium cyanide in aqueous ethanol gave both N-α-cyano-butyroylhydrazobenzene (LIV), and 4-ethyl-3-imino-5-oxo-1,2-diphenylpyrazolidine, the latter in poor yield (4%).

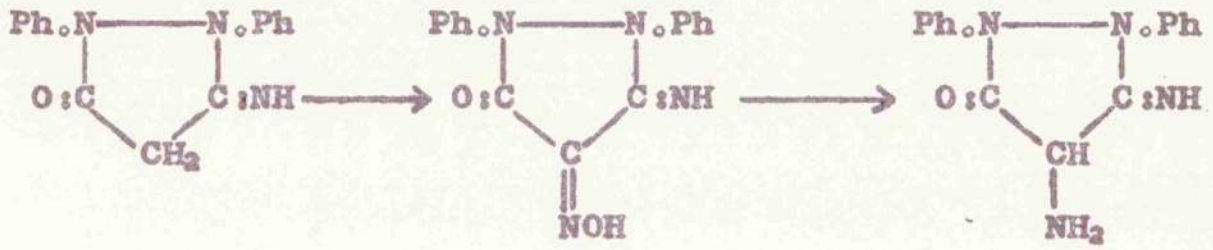
From the relatively poor yields of 4-ethyl-3-imino-5-oxo-1,2-diphenylpyrazolidine compared with 3-imino-5-oxo-1,2-diphenylpyrazolidine, and its 4-methyl homologue,[41] it is obvious that the limit of the synthetic methods is reached at the 4-ethyl derivative. After studying models of N-α-chloro and N-α-cyanoacylhydrazobenzenes, it was concluded that the above limitation can be attributed to three factors:

(a) the increasing steric inhibition of the replacement of the α-halogen atom by nitrile.

(b) the increasing difficulty of cyclisation of the N-α-cyanoacylhydrazobenzene, if formed, due to the interference of the longer side chains with the phenyl groups, when the systems are in the most favourable configuration for cyclisation.

(c) the weak basicity of the acylhydrazobenzenes. This factor can be overcome providing the steric interference is at a minimum, but in the case of N-α-chloro and N-α-cyanocaproylhydrazobenzene, it can be seen from the models that the n-butyl group interferes strongly with the phenyl groups.

The second part of the work in the pyrazolidine field, stemmed from the isolation of 4-amino-3-imino-5-oxo-1,2-diphenylpyrazolidine (LVII). The potential α-diamine system in this compound makes possible the formation of cyclic derivatives of the imino-oxo-pyrazolidine nucleus, by condensation with α-diketones and other compounds. 4-Amino-3-imino-5-oxo-1,2-diphenylpyrazolidine was synthesised by nitrosation of 3-imino-5-oxo-1,2-diphenylpyrazolidine (XXVIII) giving 4-isonitroso-3-imino-5-oxo-1,2-diphenyl-pyrazolidine (LVIII), which was subsequently reduced with zinc and hydrochloric acid.

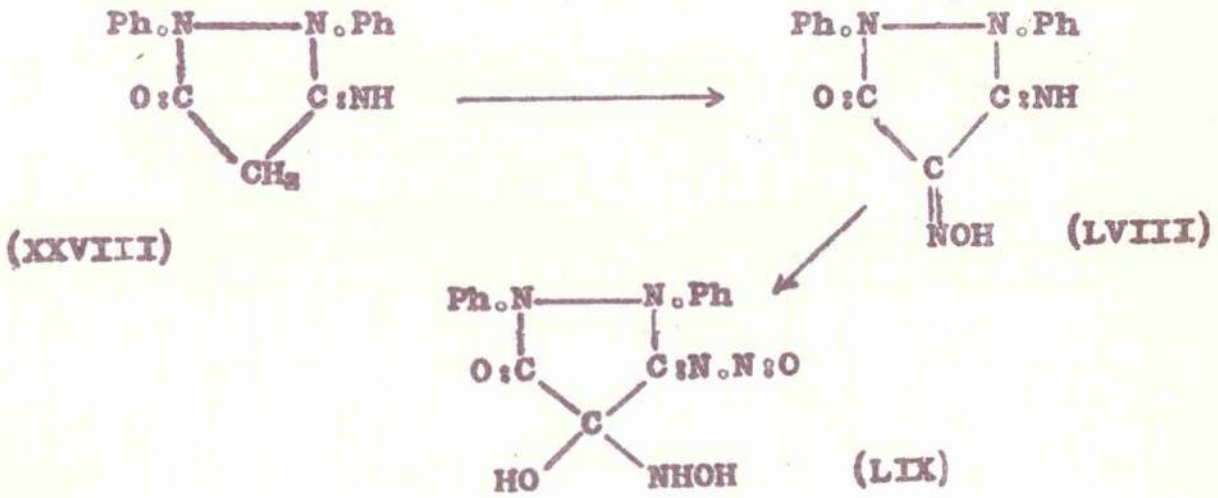


(XXVIII) (LVIII) (LVII)

However, the yield in the above nitrosation was poor, and on dilution of the mother liquors, a further product was obtained in good yield, m.p. 167° (cf. 3-imino-4-iso-nitroso-5-oxo-1,2-diphenylpyrazolidine, m.p. 247°). It was found subsequently, that by increasing the volume of ethanol in the nitrosation this latter compound was obtained as the sole product. Conversely, if the volume of ethanol was kept to a minimum the 4-isonitroso derivative (LVIII) was obtained as the major product, the second product however, still being isolated on dilution. Since the second product separated only slowly from the diluted solution, it would appear that it is formed from 3-imino-4-isonitroso-5-oxo-1,2-diphenylpyrazolidine (LVIII) by further reaction. However, no trace of this compound could be isolated after treatment of 3-imino-4-isonitroso-5-oxo-1,2-diphenylpyrazolidine with ethanolic nitrous acid. The compound gave a Liebermann test for an O- or N-nitroso group, and showed hydroxyl, and carbonyl frequency in the

infrared spectrum. The hydroxyl band was very similar to that obtained with compounds containing water of crystallisation, and this together with the evidence for the O- or N-nitroso group, and the fact that the substance is apparently formed from 3-imino-4-isonitroso-5-oxo-1,2-diphenylpyrazolidine, led to the proposed structure, 4-hydroxy-4-hydroxyamino-3-nitrosoamino-5-oxo-1,2-diphenyl pyrazolidine (LIX). Analysis agreed with this formulation.

The compound is formed presumably by further reaction of the nitrous acid with the 3-imino group with formation of an N-nitrosamine, followed by addition of water across the double bond of the isonitroso group with formation of a 'hydrated oxime'. This type of compound is a recognised intermediate in the formation of oximes, and for aldehydes and ketones with suitable electron withdrawing α-substituents, for example chloral, the hydrated oxime is relatively stable.[55]

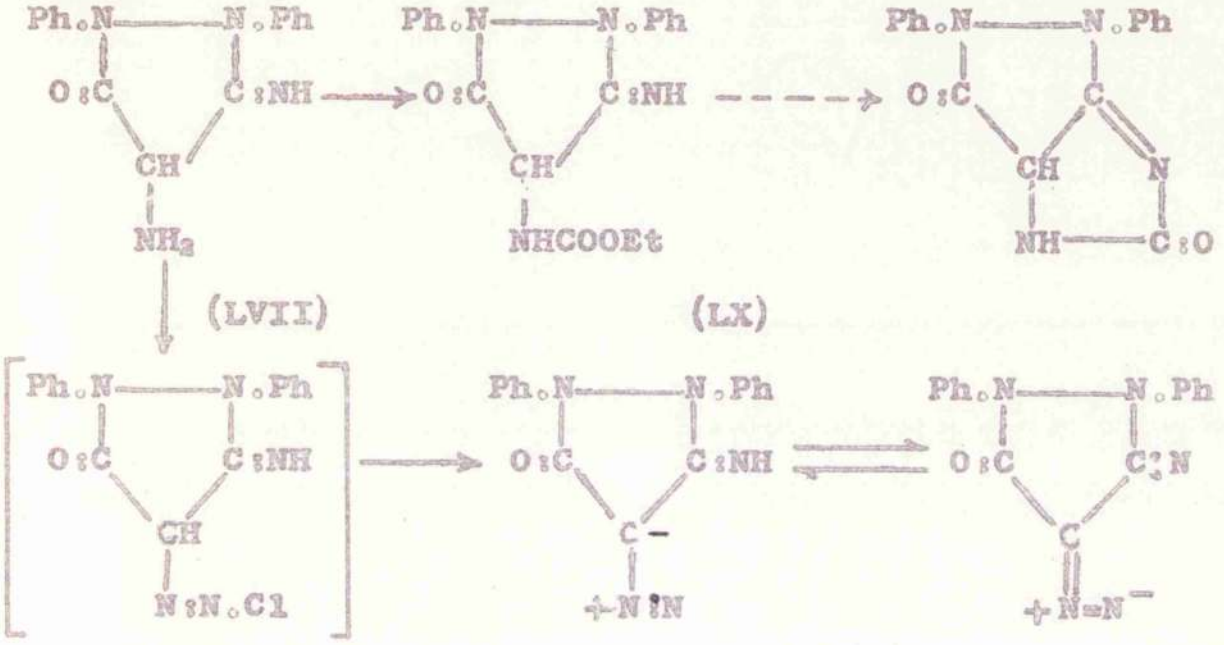


An attempted sublimation of 4-hydroxy-4-hydroxyamino-3-nitrosoamino-5-oxo-1,2-diphenylpyrazolidine (LIX), to remove water, resulted in decomposition. An attempted reduction of the above compound using zinc and hydrochloric acid, the method used to reduce the 4-isonitroso derivative, also caused decomposition.

The initial condensations of 4-amino-3-imino-5-oxo-1,2-diphenylpyrazolidine (LVII), were carried out with a view to obtaining compounds with a 5-membered ring attached to the pyrazolidine nucleus. Condensation of 4-amino-3-imino-5-oxo-1,2-diphenylpyrazolidine with ethyl chloroformate gave 4-carbethoxyamino-3-imino-5-oxo-1,2-diphenylpyrazolidine (LX) in 80% yield. However, this compound could not be cyclised by sublimation, heating in a sealed tube, or reflux with acetic anhydride, the starting material being recovered unchanged in each case.

Treatment of 4-amino-3-imino-5-oxo-1,2-diphenyl-pyrazolidine with nitrous acid precipitated a red solid, which detonates at 130°. The compound showed carbonyl, and azo group frequencies in the infrared spectrum. This, together with the explosive nature of the substance, led to the proposed structure 4-azo-3-imino-5-oxo-1,2-diphenylpyrazolidine (LXI). The absence of halogen in the molecule excludes the possibility of a diazonium salt. The reaction presumably proceeds by elimination of a molecule of hydrogen chloride between the intermediate diazonium salt, (formed by the 4-amino group) and

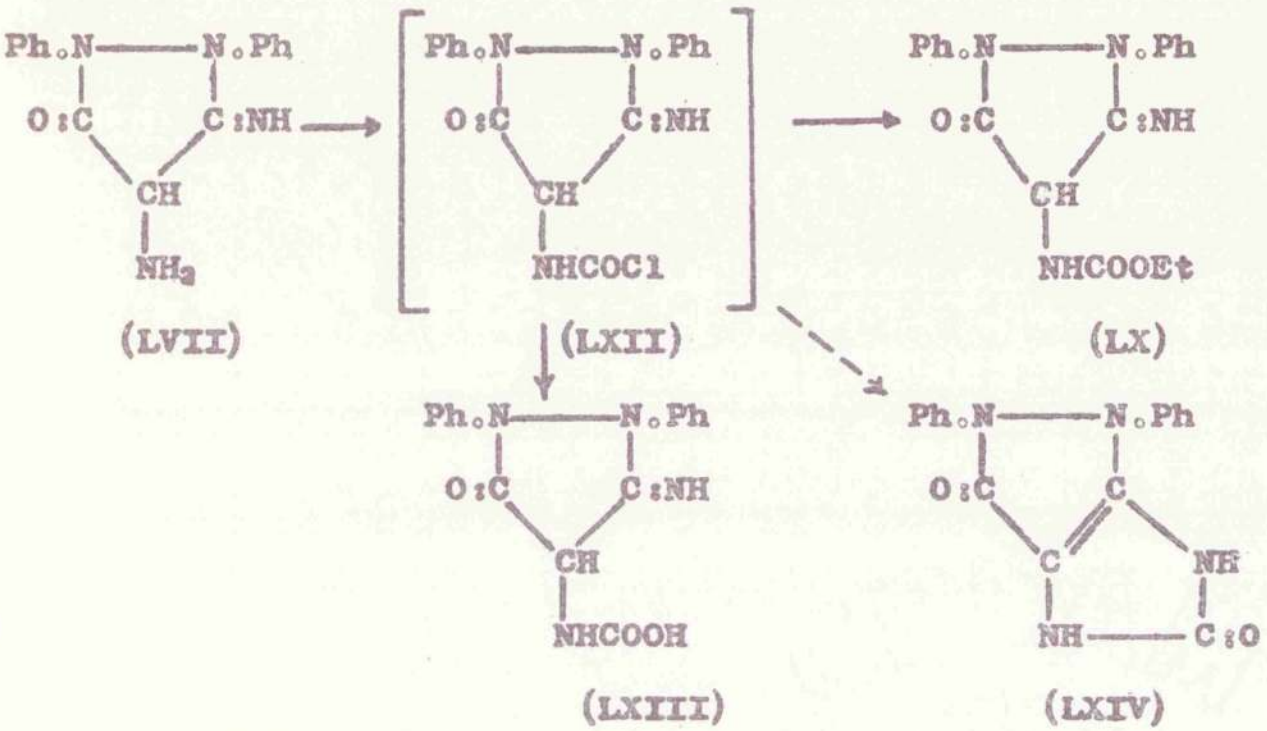
4-position. The colour of the 4-azo compound may be attributed to the various possible resonance forms.



(LVII) (LX)

(LXI)

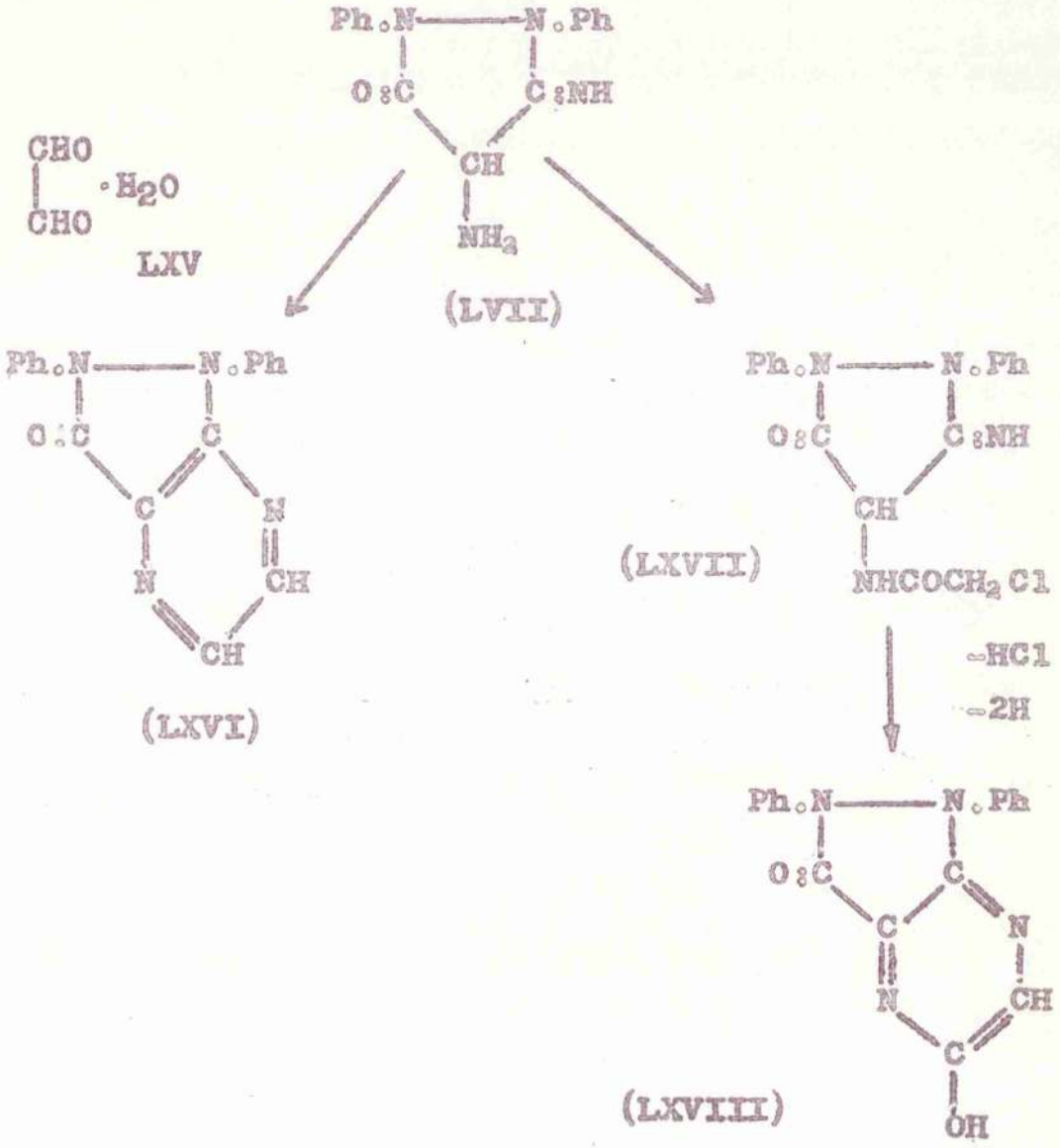
Condensation of 4-amino-3-imino-5-oxo-1,2-diphenyl pyrazolidine with carbonyl chloride in chloroform gave 4-carbethoxyamino-3-imino-5-oxo-1,2-diphenylpyrazolidine (LX), formed by the reaction of the intermediate chloroacyl amino derivative (LXII) with the ethanol present in the chloroform. This reaction appeared to occur in preference to cyclisation. Repetition of the above condensation in ethanol-free chloroform gave 4-carboxyamino-3-imino-5-oxo-1,2-diphenylpyrazolidine (LXIII), formed by hydrolysis of the intermediate chloroacyl amino derivative (LXII), in the course of isolation. A further condensation in toluene again yielded the above acid. No trace of the required imazolopyrazolidine (LXIV), was obtained.



A second series of condensations involving 4-amino-3-imino-5-oxo-1,2-diphenylpyrazolidine was carried out to form compounds with a 6-membered ring attached to the pyrazolidine nucleus. Condensation of 4-amino-3-imino-5-oxo-1,2-diphenyl-pyrazolidine (LVII) with glyoxal monohydrate (LXV) gave 5-oxo-1,2-diphenyl-3,4-pyrazinopyrazolidine (LXVI) as yellow needles (30%).

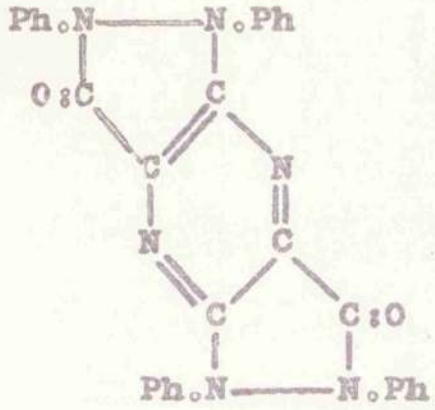
Condensation of 4-amino-3-imino-5-oxo-1,2-diphenyl pyrazolidine with chloroacetyl chloride gave 4-chloroacetyl-amino-3-imino-5-oxo-1,2-diphenylpyrazolidine (LXVII) as white needles, (25%). Attempted cyclisation of this compound, to give the pyrazine, (LXVIII) by treatment with collidine gave a trace of yellow solid m.p. 80-90°, which showed carbonyl but no

C:NH frequency in the infrared spectrum, similar to 5-oxo-1,2-diphenyl-3,4-pyrazinopyrazolidine (LXVI) above. However, insufficient material was obtained for crystallisation to analytical purity even on repetition of the condensation.

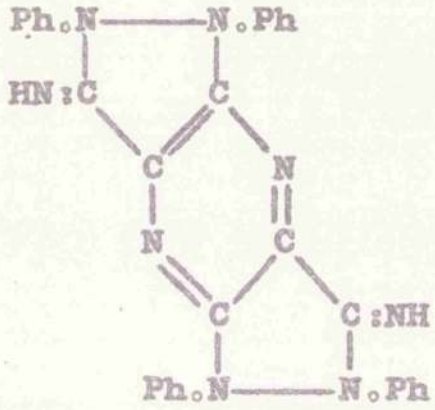


It was found that 4-amino-3-imino-5-oxo-1,2-diphenylpyrazolidine gradually deepened in colour, and on

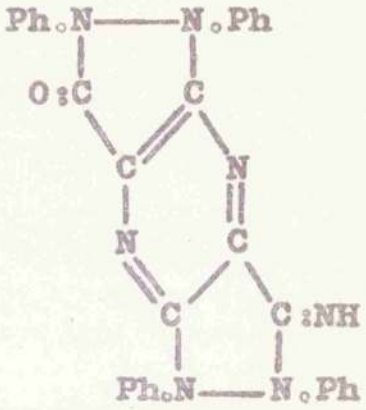
recrystallisation formed a new compound, m.p. 189° (cf 167° for the starting material). This new material was also obtained by heating a solution of 4-amino-3-imino-5-oxo-1,2-diphenylpyrazolidine in presence of platinum catalyst. This latter reaction indicated that the new compound was a self-condensation product between two molecules of the diamine giving 2,3-4,5-di-(5-oxo-1,2-diphenylpyrazolidine-3,4)-pyrazine (LXIX). It is well known that α-aminoketone compounds readily self-condense to give dihydropyrazine derivatives,[56] these being easily oxidised to the pyrazine on standing in air, so that in most cases the dihydro pyrazine cannot be isolated. In 4-amino-3-imino-5-oxo-1,2-diphenylpyrazolidine there is both an α-aminoketo function, and an aminoketoximino function, giving rise to three possible self-condensation mechanisms. A self-condensation of the α-aminoketo function giving 2,3-5,6-di-(3-imino-1,2-diphenylpyrazolidine-4,5-)-pyrazine (LXX) or, the proposed self-condensation of the α-aminoketoximino function yielding 2,3-5,6-di-(5-oxo-1,2-diphenylpyrazolidine-3,4)-pyrazine (LXIX), or a cross self-condensation giving 2,3-(3-imino-1,2-diphenylpyrazolidine-4,5)-5,6-(5-oxo-1,2-diphenylpyrazolidine-3,4)-pyrazine (LXXI), are all possible.



(LXIX)

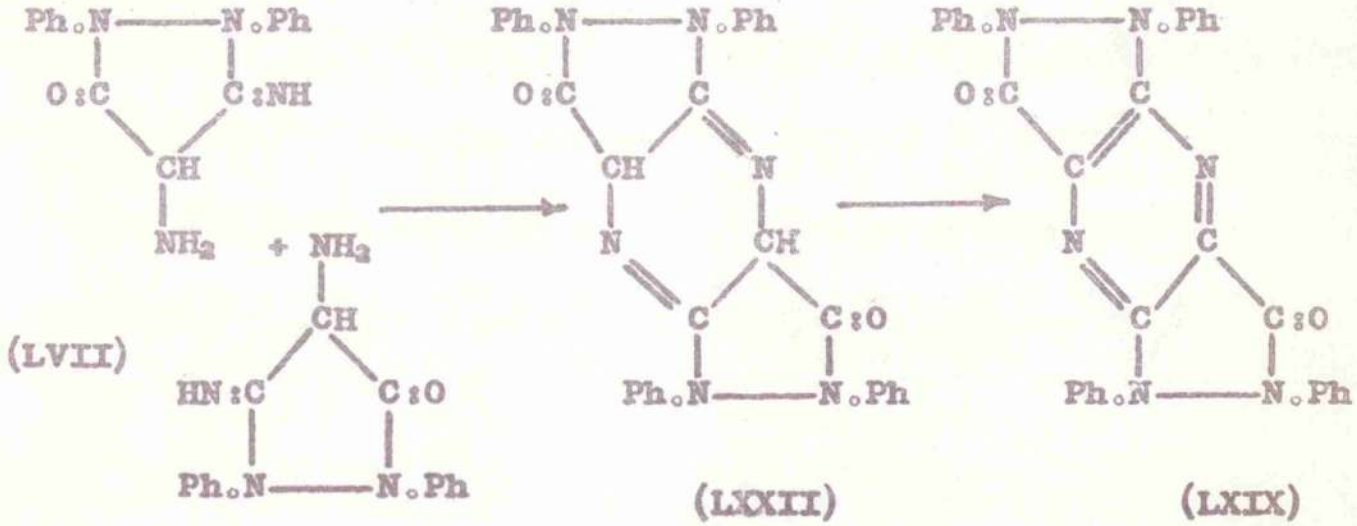


(LXX)



(LXXI)

However a nitrogen analysis can differentiate among these three possibilities, indicating that the self-condensation product is as stated, 2,3-5,6-di-(5-oxo-1,2-diphenyl-pyrazolidine-3,4)-pyrazine being formed by atmospheric oxidation of the intermediate dihydro derivative (LXXII)



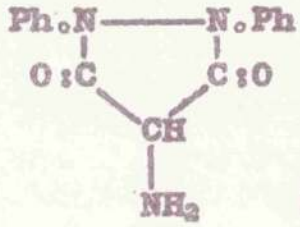
(LVII)

(LXXII)

(LXIX)

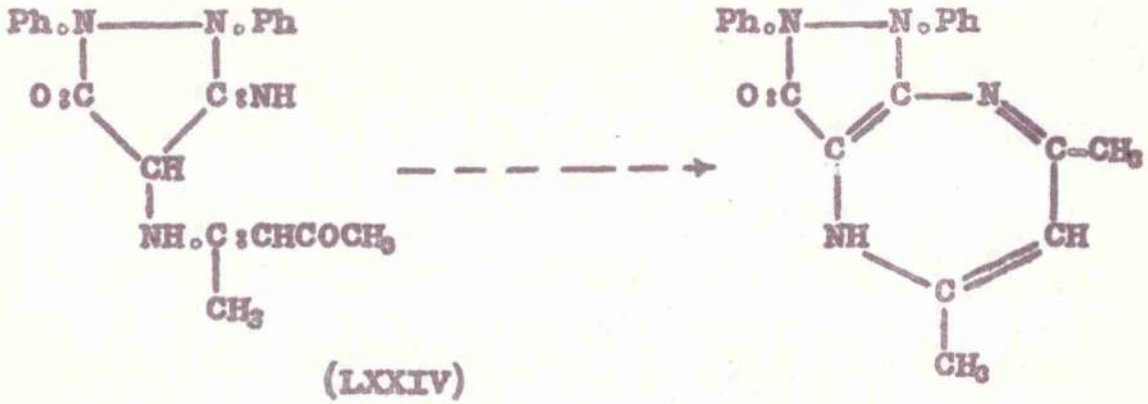
That the self-condensation takes place through the α-amino-ketoximino function is substantiated by the fact that there are no reported instances of the self-condensation of 4-amino-3,5-dioxo-1,2-diphenylpyrazolidine (LXXIII) which

contains two α-aminoketo functions similar to the one in 3-imino-5-oxo-1,2-diphenylpyrazolidine.



(LXXIII)

The final condensation with 4-amino-3-imino-5-oxo-1,2-diphenylpyrazolidine (LVII), was carried out in an attempt to obtain a seven-membered ring attached to the pyrazolidine nucleus. Condensation of 4-amino-3-imino-5-oxo-1,2-diphenylpyrazolidine with acetylacetone gave 4-acetylacetonamino-3-imino-5-oxo-1,2-diphenylpyrazolidine (LXXIV) as white plates, m.p. 218° (25%). The acyclic pyrazolidine formulation was based on the presence of two carbonyl bands in the infrared spectrum. Only one such band would be expected if cyclisation had occurred. The formulation was confirmed by analysis. Attempted cyclisations by treatment with sodium ethoxide, or acetic anhydride, failed to give any solid product, not even the starting material.



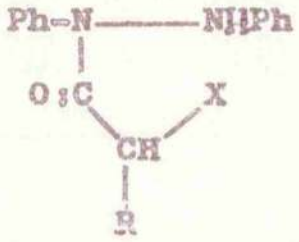
(LXXIV)

Summarising, it would appear that the inherent strain in

forming two adjacent 5-membered rings severely hinders the formation of such compounds, and explains the lack of success in this direction. The formation of such compounds in this series will also be adversely affected by the relative unreactivity of the 3-imino group. A similar explanation is offered for the non-formation of the 7-membered derivatives of the pyrazolidine. In contrast, the formation of 6-membered ring compounds attached to the pyrazolidine nucleus is not hindered to the same degree by ring strain, and this enables the unreactivity of the 3-imino group to be partly overcome, giving pyrazine derivatives of the pyrazolidines.

TABLE I

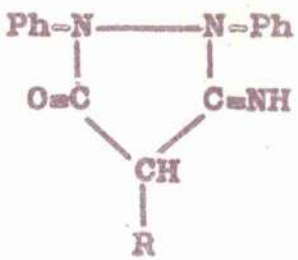
Ultraviolet absorption of N-Acylhydrazobenzenes.



Formula	R	X	$\lambda^{EtOH}_{max.}$ mμ	
XLVI	n-C_4H_9	H	205	238
XLIV	n-C_4H_9	Cl	209	236
LV	Et	H	206	236
LVI	Et	Cl	210	236
LIV	Et	C N	205	235

TABLE II

Ultraviolet absorption of 4-substituted imino-oxopyrazolidines.



Formula	R	λ_{max}^{EtOH} mμ		
XXVIII	H	206	254	
LII	Et	206	264	
LVII	NH_2	206	252	
LX	NH.COOEt	206	258	
LXVII	$NH.COCH_2Cl$	206	257	
LXI	$-N:N$	206	234	280
LXXIV	$NH.C(CH_3):CHCOCH_3$	206	262	308
L	$COCH_2CH_2CH_3$	206	256	

TABLE III

Ultraviolet absorption of cyclic 3,4-substituted imino-oxopyrazolidines.

Formula	Name	λ_{max}^{EtOH} mμ	
LXVI	5-oxo-1,2-diphenyl-3,4-pyrazinopyrazolidine	205	270
LXIX	2,3-4,5-di-(5-oxo-1,2-diphenylpyrazolidine-3,4)-pyrazine	209	234

EXPERIMENTAL

PART I

All m.p. are uncorrected. Infrared spectra were determined in Nujol unless otherwise stated. Identities were confirmed by infrared comparison in Nujol. Ultraviolet spectra in alkali, were determined in a mixture of equal parts 2N NaOH and ethanol, and in acid, equal parts 2N hydrochloric acid and ethanol. Other ultraviolet spectra were carried out in ethanol, unless otherwise stated.

Action of Raney Nickel on 4-Benzilidene-3,5-dioxo-1,2-diphenylpyrazolidine. - 4-Benzylidene-3,5-dioxo-1,2-diphenylpyrazolidine[34] (10 g.) was refluxed with Raney Nickel (11 g.) in dry ethanol (200 c.c.) for 15 min. On filtration and cooling, white crystals were obtained, m.p. 230-231° (1.5 g.). Evaporation of the ethanol produced further crops, m.p. 140-150° (2.5 g.), m.p. 145-155° (0.5 g.), and m.p. 130-140° (0.2 g.), respectively. These three crops were bulked, dissolved in chloroform, and extracted successively with saturated sodium bicarbonate solution, then 5% sodium hydroxide solution. Acidification of the bicarbonate washings yielded only a trace of oil, which would not solidify.

Acidification of the alkaline washings, yielded a white solid, which was crystallised from chloroform/methanol

as white plates of 4-benzyl-3,5-dioxo-1,2-diphenylpyrazolidine (0.5 g.) m.p. and mixed m.p. 136°. The final chloroform solution, after basic extractions, was dried and concetrated giving white needles of C-benzylmalondianilide (4.0 g.) (Found: C,76.92; H,6.07; N,8.8. $C_{23}H_{20}N_2O_2$ requires C,76.7; H,5.82; N,8.15%), λ max 207 (ε, 23,050) 250 (ε, 15,400) and 334mμ (ε, 5850); ν max. 3278 (NH or OH) and 1667 cm.$^{-1}$ (C:O).

3-Imino-5-oxo-1,2-diphenylpyrazolidine. - A solution of sodium ethoxide in ethanol, from sodium (4.5 g.) and dry ethanol (90 c.c.), was treated successively with ethyl cyanoacetate (10.6 g.), and hydrazobenzene (18 g.), and the mixture refluxed for 17 hr. in a nitrogen atmosphere (internal temperature 86-88°). Ethanol (60 c.c.) was then distilled off at normal pressure, the internal temperature rising to 126°. The reaction mixture was cooled, treated with ether (250 c.c.), and water (250 c.c.).
A pale yellow insoluble material (1 g.) separated, and this was filtered off. This solid, which had the properties of a sodium salt, was treated with hydrochloric acid (d,1.15), and the aqueous suspension extracted with chloroform. This extract, on evaporation, gave 3-imino-5-oxo-1,2-diphenyl-pyrazolidine (550 mg.), as plates m.p. 220-222° alone or mixed with an authentic specimen. The ether phase from

the initial reaction mixture, was dried (Na_2SO_4), and evaporated giving a red solid, which on crystallisation from chloroform-methanol gave hydrazobenzene (9.37 g.), as plates m.p. 126-128° (after washing with petroleum ether (b.p. 60-80°) to remove the orange colour). Evaporation of these washings gave azobenzene (2.5 g.) m.p. 67°.

The aqueous alkaline phase from the initial extraction on standing, deposited a solid (1 g.) m.p. 222°. Evaporation of this phase to one third bulk under reduced pressure, eventually gave a further crop (0.3 g.) m.p. 220°, and from the concentrated mother liquor, a further crop (0.3 g.) was obtained by extraction with chloroform (m.p. 210-220°). Combination of these crops, and crystallisation from ethanol yielded 3-imino-5-oxo-1,2-diphenylpyrazolidine (1.5 g.), m.p. 222° alone or mixed with an authentic specimen. Acidification of the concentrated alkaline liquors with 2N hydrochloric acid precipitated a brown solid m.p. 300°, which could not be crystallised, and which was not further examined.

Condensation of Cyanoacetamide with Hydrazobenzene. - Cyanoacetamide (8.4 g.), and hydrazobenzene (18.4 g.) were refluxed for 65 hr. in a nitrogen atmosphere, with sodium ethoxide, from sodium (4.6 g.) and dry ethanol (100 c.c.). Ammonia was evolved on reflux. The mixture was then cooled, and water, and ether added. No interfacial solid separated,

and the two layers were separated, the ether phase on drying and evaporating giving a white solid, which on recrystallisation from chloroform gave hydrazobenzene (12.3 g.) m.p. 126-128°, after washing with petroleum ether (b.p. 60-80°) The petroleum washings on evaporation gave azobenzene (7.2g.) m.p. 67°.

The basic aqueous phase was acidified yielding a brown solid (2.5 g.) not melting below 350°, which was not investigated further. No trace of 3-imino-5-oxo-1,2-diphenylpyrazolidine was obtained.

Chloroacetylhydrazobenzene. - α-Chloroacetyl chloride (40 g.) in chloroform (30 c.c.) was added dropwise, with stirring, to an ice-cooled solution of hydrazobenzene (25 g.) in chloroform (250 c.c.), and pyridine (150 c.c.). Stirring was continued for a further 2 hr. and the chloroform solution was then washed successively with 2N hydrochloric acid, 2N sodium hydroxide solution, water, and dried (Na_2SO_4). N-α-chloroacetylhydrazobenzene (58 g.)[57] was obtained on evaporation of the chloroform as prisms, m.p. 163° (lit., m.p. 163°).

Cyclisation of the Above Compound. - A solution of chloroacetylhydrazobenzene (3.4 g.), in ethanol (50 c.c.), was refluxed for 7 hr. with a solution of potassium cyanide

(6 g.), in water (50 c.c.). The solution was then cooled, diluted with water, and extracted with chloroform. The chloroform solution was washed thoroughly with water, dried, and reduced in bulk, giving 3-imino-5-oxo-1,2-diphenyl-pyrazolidine (1.1 g.), m.p. and mixed m.p. with an authentic specimen 220-222°.

3-Imino-5-oxo-1,2-di-p-tolylpyrazolidine. - Ethyl cyanoacetate (10.6 g.) and hydrazotoluene (21 g.) were refluxed for 17 hr. in a nitrogen atmosphere with sodium ethoxide, from sodium (4.8 g.) and dry ethanol (150 c.c.). Ethanol (100 c.c.) was then distilled off, and the resultant sludge extracted with ether, and water. An interfacial solid was obtained, and this was filtered off. Additional solid separated from the basic aqueous phase, and this was added to the interfacial solid. The combined solids were recrystallised from chloroform-methanol, as white plates, m.p. 213°, of 3-imino-5-oxo-1,2-di-p-tolylpyrazolidine (1.2 g.) (Found: C, 72.76; H, 5.95; N, 14.57. $C_{17}H_{17}N_3O$ requires C, 73.09; H, 6.13; N, 15.04%), λ max. 207 (ε, 52,000) and 254 mμ (ε, 29,500); νmax 3390, 3185 (NH or OH), 1675 and 1647 cm.$^{-1}$ (C:O or C:NH). The ether phase was dried, and concentrated, giving a bright orange solid. This was thoroughly washed with petroleum ether (b.p. (40-60°), leaving a residual off-white solid, which was crystallised from chloroform-petroleum

ether, as white plates of hydrazotoluene (10.6 g.) m.p. 128°. The combined petroleum washings yielded azotoluene (6.1 g.) m.p. 142°. The basic phase was continuously extracted with chloroform for 5 hr., the extract on concentration giving a viscous black oil, from which no solid could be obtained. After extraction, the basic phase was acidified, precipitating a brown solid (1.8 g.) m.p. 320° (partial). This solid could not be crystallised, and no further work was carried out on it.

4-Benzylidene-3-imino-5-oxo-1,2-di-p-tolylpyrazolidine. - 3-Imino-5-oxo-1,2-di-p-tolylpyrazolidine (0.5 g.) was refluxed in benzaldehyde (2.5 c.c.) for 1 hr. The mixture was cooled, and diluted with ether when 3-imino-5-oxo-1,2-di-p-tolylpyrazolidine (0.35 g.), m.p. and mixed m.p. 213° separated out, and was filtered off. The ethereal solution was washed with sodium metabisulphite solution to remove excess aldehyde, and then with water, dried, and the ether removed under reduced pressure. A red gum was obtained which, on treatment with petroleum ether (b.p. 40-60°), eventually gave a yellow solid, which was crystallised from chloroform-methanol to give 4-benzylidene-3-imino-5-oxo-1,2-di-p-tolylpyrazolidine (0.1 g.) as yellow felted needles m.p. 280° (Found: C, 77.96; H, 5.31; N, 11.44: $C_{24}H_{21}N_3O$ requires C, 78.45; H, 5.76; N, 11.4%), $\lambda_{max.}$ 208 (ε, 36,800), 292 (ε, 35,300)

and 362 mμ (ε, 5,000); $\nu_{max.}$ 1710 $cm.^{-1}$ (C:O).

Attempted Synthesis of 3,5-di-imino-1,2-diphenyl-pyrazolidine. - (a) Malononitrile (6.6 g.) and hydrazobenzene (18.4 g.) were refluxed for 17 hr. in a nitrogen atmosphere with sodium ethoxide, from dry ethanol (100 c.c.) and sodium (4.6 g.). Ethanol (80 c.c.), was then distilled off, and the resultant sludge was diluted with ether, and water. No interfacial solid separated, and the two phases were separated. The ether solution was washed with water, dried and concentrated giving an orange solid, which on crystallisation from chloroform-petroleum ether (b.p. 40-60°) gave white plates of hydrazobenzene (15.7 g.), after washing with petroleum ether. The combined petroleum washings were evaporated giving azobenzene (0.7 g.), m.p. 67°. Malononitrile (3 g.) was isolated from the mother liquors. No other solid was isolated.

The basic aqueous phase was acidified, precipitating a trace of brown material which did not melt below 300°. This was not investigated further.

(b) A similar experiment in which the reflux time was extended to 160 hr. again yielded azobenzene and hydrazobenzene as the sole crystalline products.

Condensation of Ethyl n-Butylcyanoacetate with Hydrazobenzene. - Ethyl n-butylcyanoacetate[58] (16.3 g.) and hydrazobenzene (18.4 g.) were refluxed for 17 hr. in a nitrogen atmosphere with a molar quantity of sodium ethoxide, from sodium (4.6 g.) and dry ethanol (200 c.c.). Ethanol (100 c.c.) was then distilled off, and the residue extracted with ether, and water. The ether phase was washed with water, dried, and concentrated giving an orange solid, which on crystallisation from chloroform gave plates of hydrazobenzene (6.5 g.), m.p. and mixed m.p. 124-126° after washing with petroleum ether (b.p. 40-60°). The petroleum washings yielded azobenzene (5.3 g.), m.p. 67°. No other solid could be isolated. The basic aqueous phase was acidified giving a pale yellow oil, which was extracted with chloroform. The oil obtained on evaporation of the extract was bicarbonate soluble, and was proved to be n-butylcyanoacetic acid (12 g.). No trace of the condensation product was obtained.

n-Butylcyanoacetyl Chloride. - n-Butylcyanoacetic acid (2 g.) was refluxed for 2 hr. with an excess of thionyl chloride. The excess of thionyl chloride was then distilled off under reduced pressure, and the residue was used in the following condensation, without attempting a

distillation. [A small portion of the residue was treated with an excess of aqueous ammonia giving a white solid, which crystallised from chloroform-petroleum ether (b.p. 60-80°) as white needles of n-butylcyanoacetamide, m.p. 124-125° (lit., m.p. 125°)].

The remainder of the residue (2 c.c.) was added to an ice-cooled solution of hydrazobenzene (1 g.) in chloroform-pyridine 15 c.c. 2 c.c.). The mixture was allowed to stand for 2 hr., and was then washed successively with 2N hydrochloric acid, 2N sodium hydroxide solution, and water. A solid was precipitated during the acid washing, and this was filtered off, and treated with a saturated solution of sodium bicarbonate, filtered again, dried and crystallised from ether as white plates of benzidine (0.7 g.), m.p. and mixed melting point 127°. The final chloroform solution, after washing, was dried and evaporated to dryness giving a red oil, from which no solid other than a trace of azobenzene could be isolated. Acidification of the caustic washings gave the starting acid (0.6 g.).

The above condensation was repeated with a 3:1 ratio of acyl chloride to hydrazobenzene. Azobenzene and hydrazobenzene were obtained as the sole crystalline products.

Condensation of α-Bromocaproyl Bromide with Hydrazobenzene.- (a) Using Pyrine. α-Bromocaproyl bromide[59] (30 g.) was added slowly to an ice-cooled, stirred solution of hydrazobenzene (20 g.) in chloroform-pyridine (100 c.c.-40 c.c.). Stirring was continued for a further 2 hr., and the mixture was then washed successively with 2N hydrochloric acid, 2N sodium hydroxide solution, and water. The chloroform solution was dried and evaporated to dryness giving a red gum, from which no solid other than azobenzene (5.2 g) could be obtained, even after extensive treatment with a variety of solvents. The gum was then refluxed with an excess of potassium cyanide (20 g.) in aqueous ethanol for 7 hr., water was added, and red oil was precipitated. This was extracted with chloroform, and on drying, and concentrating the chloroform solution a red gum was obtained, which on extensive treatment with acetone-petroleum ether (b.p.60-80°) gave a white solid, recrystallised from methanol as white plates of N-n-caproylhydrazobenzene, m.p. 121° (2 g.) (Found: C, 76.2; H, 7.92. $C_{18}H_{22}N_2O$ requires C, 76.56; H, 7.85%), λ max.205 (ε, 4,500) and 238 mμ (ε, 18,500); ν max 3226 (NH) and 1653 cm.$^{-1}$ (C:O) (This formulation was confirmed, by a mixed m.p. with an authentic specimen, synthesised from caproyl chloride and hydrazobenzene). α-Bromocaproic acid (8 g.) and azobenzene (4 g.) were isolated from the mother liquors.

(b) Using Dimethylaniline. - Repetition of the above condensation using dimethylaniline as the basic medium once again gave a red oil. This on treatment with potassium cyanide solution gave N-n-caproylhydrazobenzene and azobenzene as the sole crystalline products. The mother liquors of the reaction gave a red colour with ferric chloride solution, characteristic of the imino-oxo series, but no solid could be obtained.

(c) Using an Excess of Acyl Bromide. - A further condensation was carried out using an excess of α-bromo-caproyl bromide. A pale yellow solid m.p. 150-60° (50 mg.) giving a positive Beilstein test for halogen but showing no carbonyl frequency in the infrared spectra, was obtained. Azobenzene was also isolated, these being the sole crystalline products. The residue was not treated with potassium cyanide.

(d) By Addition of the Hydrazobenzene to the Acyl Bromide. - Hydrazobenzene (2 g.) in chloroform-pyridine (20 c.c.-5 c.c) was added to an ice-cooled solution of α-bromocaproyl bromide (4 g.) in chloroform (10 c.c.) over a period of 30 min. The mixture was allowed to stand for a further 2 hr., and was then washed with 2N hydrochloric acid, 2N sodium hydroxide solution, and water. The final chloroform solution was dried, and evaporated to dryness giving a red oil, from which no solid could be isolated. The oil was subsequently

refluxed for 7 hr., with an aqueous ethanolic solution of potassium cyanide (5 g.). The reaction mixture was extracted with chloroform, the chloroform solution being thoroughly washed with water, dried, and evaporated to dryness giving a red oil. This oil was chromatographed in an attempt to remove azobenzene. However, no solid other than azobenzene was isolated, although several fractions gave a red colour with ferric chloride solution.

A repetition of the above condensation (d) on a larger scale, again yielded azobenzene as the sole crystalline product.

(e) In Ether. - Hydrazobenzene (5 g.) and α-bromocaproyl bromide (7 g.) were separately dissolved in ether (50 c.c.), and the solutions mixed. Benzidine hydrobromide was precipitated, and the mixture was refluxed for 1 hr., cooled, and washed free of the hydrobromide, with water. The ether phase was dried, and the ether removed by distillation, giving a red oil. This was kept at 0° for 24 hr., but no solid separated and the oil was refluxed for 7 hr., with an aqueous ethanolic solution of potassium cyanide (7 g.). The mixture was then extracted with chloroform, and on washing, drying, and evaporating off the chloroform a red gum was obtained, from which no solid

other than azobenzene could be isolated. The oil did not give a red colour with ferric chloride solution.

Condensation of α-Bromocaproyl Chloride with Hydrazobenzene. - α-Bromocaproic acid[60] (30 g.) was refluxed for 1 hr., with an excess of thionyl chloride. The excess of thionyl chloride was then distilled off under reduced pressure, and the α-bromocaproyl chloride (20 g.) was finally distilled at 65°/9 mm.

(a) In Ether. - A solution of hydrazobenzene (4.6 g.) in ether (35 c.c.) was refluxed for 1 hr. with a solution of α-bromocaproyl chloride (5 g.) in ether (150 c.c.). Benzidine hydrochloride was precipitated, and was filtered off. The ether was washed with water, dried, and evaporated off giving a brown oil from which no solid could be isolated.

(b) In Chloroform-pyridine. - To hydrazobenzene (4 g.) in chloroform-pyridine (30 c.c.-8 c.c.), a solution of α-bromocaproyl chloride (5 g.) in chloroform (10 c.c.) was added, the mixture being cooled on an ice-bath. The mixture was then stirred for 2 hr., and allowed to stand overnight. The chloroform solution was washed successively with 2N hydrochloric acid, 2N sodium hydroxide solution, and water, dried, and the chloroform distilled off under reduced pressure, giving a red-brown solid from which no solid other

than azobenzene could be isolated.

The above condensation was repeated without cooling during the addition of the acyl chloride. A gum was obtained which on subsequent treatment, with potassium cyanide solution gave azobenzene, and N-n-caproylhydrazobenzene as the sole crystalline products.

Action of Sulphuryl Chloride on Caproyl Chloride. - Caproyl chloride (20 g.) was refluxed with sulphuryl chloride (50 c.c.) for 18 hr., in presence of a trace of iodine, as promoter. Fractional distillation of the reaction mixture gave the starting materials, together with a small trace of caproic acid formed by hydrolysis. No trace of the required α-chlorocaproyl chloride was obtained.

Action of Phosphorus Trichloride on Caproic Acid. - Caproic acid (116 g.), and phosphorus trichloride (20 c.c.) were mixed and heated to 120°. Chlorine was then bubbled slowly through the mixture for 17 hr. Fractional distillation of the reaction mixture gave the starting materials together with a trace of the required α-chlorocaproic acid.

Adaptation of the Above Process. - Caproic acid (50 g.) was heated to 140° with phosphorus trichloride (50 c.c.), in presence of a trace of caproyl chloride as promoter. Chlorine was slowly bubbled through the mixture

for 17 hr., and the mixture was then fractionally distilled under reduced pressure giving fractions as follows:-

1. b.p. 52-66° at 10 mm.
2. b.p. 66-80° at 15 mm.
3. b.p. 110° at 15 mm.

The second fraction was redistilled giving an acyl chloride (55 g.) b.p. 170-174° (atmos.), (cf. caproyl chloride b.p. 153°). Vapour phase chromatography showed that the material differed from caproyl chloride, and that it was a single compound. The amide was formed by addition of the chloride to aqueous ammonia, and crystallised from ethanol as white plates of a mono-chlorocaproyl amide m.p. 57°. (Found: C, 48.35; H, 7.5: $C_6H_{12}ClNO$ requires C, 48.2; H, 8.05%). The material gave a positive Beilstein test for halogen. A comparison of boiling points of chloroacyl chlorides in the homologous series indicated that the chlorine atom in the above compound is in the α-position.

Propionyl chloride	b.p. 80°	ΔT 35°
α-Chloropropionyl chloride	115°	ΔT 29°
β-Chloropropionyl chloride	144°	
Butyryl chloride	101°	ΔT 29°
α-Chlorobutyryl chloride	130°	
Caproyl chloride	153°	ΔT 21°
α-Chlorocaproyl chloride	174	

Condensation of α-Chlorocaproyl Chloride with Hydrazobenzene. - α- Chlorocaproyl chloride (20 g.) was added dropwise to a stirred ice-cooled solution of hydrazobenzene (10 g.) in chloroform-pyridine (60 c.c.-30 c.c.). The addition took place over 1½ hr., and stirring was kept at 0° for 16 hr., then washed with 2N hydrochloric acid 2N sodium hydroxide solution and water. On drying concentrating the chloroform solution a red oil was obtained which, on treatment with acetone-petroleum ether (b.p. 60-80°) eventually gave α-chlorocaproylhydrazobenzene (11 g.) as white plates, recrystallised from methanol, m.p. 85°, (Found: C,68.17; H,6.67; N,8.57. $C_{18}H_{21}ClN_2O$ requires C,68.23; H,6.68; N,8.84%), λ max. 209 (ε, 20,000) and 236 mμ (ε, 18,800); ν max. 3226 (NH) and 1666 $cm.^{-1}$ (C:O).

Attempted Cyclisation of α-Chlorocaproylhydrazobenzene using Potassium Cyanide. - (a) α-Chlorocaproylhydrazobenzene (5 g.) was dissolved in ethanol (50 c.c.), and a solution of potassium cyanide (10 g.) in water (50 c.c.) was added, the mixture being refluxed for 7 hr. Water was then added, and the mixture extracted with chloroform, the chloroform extract being washed with water, dried, and evaporated to dryness giving a viscous red gum (1 g.), from which no solid other than azobenzene could be isolated, even on chromatography. The aqueous ethanolic solution was carefully acidified with

dilute nitric acid, and the liberated hydrogen cyanide was boiled off. The resultant aqueous solution gave a precipitate with silver nitrate solution showing that the chlorine had been displaced. A chloroform extract of the acidified solution however, gave only a trace of solid not melting before 350°.

(b) The above reaction was repeated using α-chlorocaproylhydrazobenzene (2 g.), and potassium cyanide (10 g.). On treatement as above, azobenzene was obtained as the sole crystalline product.

(c) Further repetition of the above reaction using α-chlorocaproylhydrazobenzene (8 g.), and potassium cyanide (10 g.) again gave azobenzene as the sole crystalline product.

Attempted Formation of α-Cyanocaproylhydrazobenzene.

(a) Using Potassium Cyanide-Copper Sulphate. - α-Chlorocaproylhydrazobenzene (2 g.) in ethanol (20 c.c.) was refluxed for 4 hr. with a mixture of potassium cyanide (5 g.), and copper sulphate (4 g.), in water (15 c.c.). The mixture was cooled and extracted with chloroform, and on drying and concentrating the chloroform solution the starting material (1.9 g.) m.p. and mixed m.p. 84-85° was obtained. No other product was isolated.

(b) Using Silver Cyanide. - α-Chlorocaproylhydrazobenzene (2 g.) was refluxed for 4 hr. in toluene (50 c.c.) with solid silver cyanide (10 g.). The mixture was then filtered, and the toluene distilled off under reduced pressure giving α-chlorocaproylhydrazobenzene (2 g.), m.p. and mixed m.p. 85°. No other product was isolated.

(c) Using Liquid Hydrogen Cyanide. - A solution of α-chlorocaproylhydrazobenzene (8 g.), in liquid was allowed to stand for 24 hr. Chloroform was then added to the mixture, and the chloroform solution washed thoroughly with water, dried and concentrated giving α-chlorocaproyl-hydrazobenzene (7.9 g.), m.p. and mixed m.p. 84-85°. No other product was isolated.

4-Butyroyl-3-imino-5-oxo-1,2-diphenylpyrazolidine. - To a cooled solution of 3-imino-5-oxo-1,2-diphenylpyrazolidine (2 g.) in dioxan-pyridine (20 c.c.-5 c.c.), butyroyl chloride (3 c.c.) was slowly added over ½ hr., with stirring. The stirring was continued for a further 2 hr., chloroform was then added, and the chloroform solution was washed successively with 2N hydrochloric acid, 2N sodium hydroxide solution, and water. On drying, and evaporating off the chloroform, a gum was obtained, from which solid was obtained on treatment with acetone. This solid was crystallised from chloroform-

methanol as white plates, m.p. 306-307° of 4-butyroyl-3-imino-5-oxo-1,2-diphenylpyrazolidine (15 mg.), (Found: C,70.85; H,5.8. $C_{20}H_{19}N_3O_2$ requires C,71.03; H,5.92%), λ max 206 (ε, 33,700) and 256 mμ (ε, 26,000); ν max. 3226, 3125 (NH or OH) and 1613 $cm.^{-1}$ (C:O).

3-Imino-5-oxo-1,2-diphenylpyrazolidine (0.7 g.) was eventually isolated from the mother liquors.

Attempted Reduction of 4-Butylidene-3-imino-5-oxo-1,2-diphenylpyrazolidine. - 4-Butylidene-3-imino-5-oxo-1,2-diphenylpyrazolidine[50] (0.5 g.) was added slowly to a vigorously stirred mixture of concentrated hydrochlorid acid (10 c.c.), ice (25 g.), and zinc dust (2 g.). The mixture was stirred for 2 hr., filtered free from the excess of zinc, and extracted with ether. The ether was washed with water, dried, and distilled off giving the starting material (0.47 g.), m.p. and mixed m.p. 194°.

Condensation of α-Ethylcyanoacetyl Chloride with Hydrazobenzene.

Preparation of α-Ethylcyanoacetyl Chloride.

Ethyl-α-ethylcyanoacetate[61] (20 g.) was shaken with 10% sodium hydroxide solution (40 c.c.), and the resultant solution was acidified to Congo red with dilute hydrochloric acid. The aqueous solution was extracted with ether, and on drying, and evaporating off the ether, α-ethylcyanoacetic

acid (15 g.) was obtained. This acid was refluxed for 2 hr. with an acess of thionyl chloride (4 0 c.c.), the excess of reagent was then distilled off under reduced pressure, and finally α-ethylcyanoacetyl chloride (5 c.c.) was carefully distilled, (b.p. 46-48°/0.5 mm.).

(a) α-Ethylcyanoacetyl chloride (1 c.c.) was added to a stirred ice-cooled solution of hydrazobenzene (0.5 g.) in chloroform-pyridine (20 c.c.-2 c.c.), the mixture being kept at 0° for 24 hr., before washing with 2N hydrochloric acid, 2N sodium hydroxide solution, and water. Neither the acidic nor basic washings yielded any material on neutralisation. The final chloroform solution was dried, and concentrated giving N-α-cyanobutyroylhydrazobenzene (120 mg.) as white plates, m.p. 104° (Found: C, 73.42; H, 6.26; N, 15.74. $C_{17}H_{17}N_3O$ requires C, 73.0 ; H, 6.13; N, 15.04%), λ max. 206 (ε, 29,300) and 235 mμ (ε, 23,000); ν max 3260 (NH), 2220 (C:N) and 1652 $cm.^{-1}$ (C:O).

(b) The above condensation was repeated on a larger scale, and using a 3:1 molar ratio of acyl chloride to hydrazobenzene No N-α-cyanobutyroylhydrazobenzene was isolated. A solid m.p. 350° and azobenzene were obtained as the only solid products.

The mother liquors of the reaction gave a red colour with ferric chloride solution.

Attempted Cyclisation of α-Cyanobutyrylhydrazobenzene.- α-Cyanobutyroylhydrazobenzene (60 mg.) was refluxed for 2 hr. with a 2N solution of sodium carbonate in 1:1 ethanol-water (10 c.c.). The mixture was then cooled and extracted with chloroform, and on drying, and distilling off the chloroform, an oil was obtained from which no solid, other than a trace of the starting material, was isolated. The oil did not give a red colour with ferric chloride solution.

Condensation of α-Chlorobutyroyl Chloride with Hydrazobenzene. - α-Chlorobutyroyl chloride (15 g.), prepared by refluxing butyroyl chloride with sulphuryl chloride in the presence of a trace of iodine, was added dropwise to a stirred, ice-cooled solution of hydrazobenzene (8 g.) in chloroform-pyridine (50 c.c.-20 c.c.). Stirring was continued for a further 2 hr. and the mixture was allowed to stand overnight. Water was then added, and the chloroform solution was washed successively with 2N hydrochloric acid, 2N sodium hydroxide solution, and water. On drying, and distilling off the chloroform a red gum was obtained, from which no solid, other than azobenzene, could be obtained. The gum was refluxed with a solution of potassium cyanide (20 g.) in aqueous ethanol. The mixture was then diluted water, and thoroughly extracted with chloroform. The chloroform extract was dried and concentrated giving a red

gum, which on treatment with acetone-petroleum ether (b.p. 40-60°) gave N-n-butyroylhydrazobenzene (2 g.), m.p. 115-120°, (Found: C, 75.3; H, 7.04; N, 10.76. $C_{16}H_{18}N_2O$ requires C, 75.63; H, 7.08 N, 11.03%), λ max 208 (ε, 17,500) and 236 mu (ε, 18,500) ν max. 3278 (NH) and 1647 $cm.^{-1}$ (C:O). The identity of the material was confirmed by synthesis of an authentic specimen of N-n-butyroylhydrazobenzene from butyroyl chloride and hydrazobenzene, m.p. and mixed m.p. 120°.

A further solid (50 mg.), m.p. 204°, was also isolated from the mother liquors of the reaction. This was 4-ethyl-3-imino-5-oxo-1,2-diphenylpyrazolidine, (Found: C, 72.62; H, 6.11; N, 15.1 $C_{17}H_{17}N_3O$ requires C, 73.09; H, 6.13; N, 15.04%), λ max. 206 (ε, 29,400) and 264 mu (ε, 27,000); ν max. 3449, 3279 (NH or OH) and 1626, 1640 $cm.^{-1}$ (C:O and C:NH). The compound was recrystallised from ethanol, m.p. 206°. It gave a red colour with ferric chloride solution.

(b) The above condensation was repeated with very slow addition of the α-chlorobutyroyl chloride (10 g.) to the hydrazobenzene (14 g.) in chloroform-pyridine (100-20 c.c.). On treatment as above, α-chlorobutyroylhydrazobenzene (10 g.) was isolated as white plates, after a recrystallisation from chloroform-methanol, m.p. 128°, (Found: C, 66.6; H, 6.04. $C_{16}H_{17}ClN_2O$ requires C, 66.55; H, 5.89%), λ max. 210 (ε, 15,400) and 236 mu (ε, 16,600); ν max. 3280 (NH) and

1660 cm.$^{-1}$ (C:O). The compound gave a positive Lassaigne test for chlorine.

Cyclisation of α-Chlorobutyroylhydrazobenzene. - (a) α-Chlorobutyroylhydrazobenzene (0.5 g.) was refluxed for 7 hr. with potassium cyanide (5 g.) in aqueous ethanol. The reaction mixture was then extracted with chloroform and the chloroform solution was dried, and concentrated giving a red gum, from which 4-ethyl-3-imino-5-oxo-1,2-diphenyl pyrazolidine (20 mg.), m.p. and mixed m.p. 206° was isolated. No solid except the above and azobenzene (0.2 g.) was obtained.

(b) The cyclisation was repeated on a larger scale, and the gum obtained was chromatographed on alumina. Petroleum ether, and petroleum ether-benzene eluted azobenzene (300 mg.) Benzene eluted N-α-cyanobutyroylhydrazobenzene (50 mg.) identified by mixed m.p. with an authentic specimen. 4-Ethyl-3-imino-5-oxo-1,2-diphenylpyrazolidine (100 mg.) was obtained from the final fractions eluted with ether, and ether-methanol.

3-Imino-4-isonitroso-5-oxo-1,2-diphenylpyrazolidine. 3-Imino-5-oxo-1,2-diphenylpyrazolidine (5 g.) was dissolved in a minimum of ethanol (10 c.c.), and crushed ice (50 g.) was added, followed by 2N hydrochloric acid (250 c.c.). A 2N solution of sodium nitrite (250 c.c.) was slowly added.

A pink solid separated out, was filtered off, and crystallised from tetrahydrofuran-petroleum ether as dark red needles of 3-imino-4-isonitroso-5-oxo-1,2-diphenylpyrazolidine (2.9 g.), m.p. 247°, (Found: C,64.2; H,4.1; N,19.7. $C_{15}H_{12}N_4O_2$ requires C,64.4; H,4.29; N,20.0%), λ max. 208 (ε, 19,500), 319 (ε, 16,000) and λ inflex. 228 mμ (ε, 17,000); ν max. 3226 (NH or OH), 1670 and 1712 cm.$^{-1}$ (C = O). The mother liquors of the above reaction were diluted with water, and allowed to stand for 24 hr. A white solid separated out, and this was filtered off, and crystallised from tetrahydrofuran-petroleum ether as white prisms of 4-hydroxy--4-hydroxyamino-3-nitrosoamino-5-oxo-1,2-diphenylpyrazolidine (1.8 g.), m.p. 168°, (Found: C,54.89; H,4.03; N,20.82. $C_{15}H_{13}N_5O_4$ requires C,55.05; H,3.98; N,21.4%) λ max. 210 (ε, 17,400), 219 (ε, 16,250) and 280 mμ (ε, 4,000); νmax 3450 (OH) 3218 (NH) and 1702 cm.$^{-1}$ (C:O). The compound gave a positive Liebermann test for an N-nitroso group. An attempted high vacuum sublimation resulted in decomposition.

Repetition of the Above in Excess Ethanol. - 3- Imino -5-oxo-1,2-diphenylpyrazolidine (2 g.) was dissolved in ethanol (50 c.c.), and crushed ice (50 g.) was added followed by 2N hydrochloric acid (250 c.c.). A 2N solution of sodium nitrite (250 c.c.) was added slowly to the mixture. No solid separated, and the solution was diluted with water

(500 c.c.), and allowed to stand for 24 hr. The material obtained above (1.9 g.), m.p. 168° was obtained again m.p. and mixed m.p. 167-168°. No 3-imino-4-isonitroso-5-oxo-1,2-diphenylpyrazolidine was isolated.

Attempted Synthesis of the Above Compound from 3-Imino-4-isonitroso-5-oxo-1,2-diphenylpyrazolidine. - 3-Imino-4-isonitroso-5-oxo-1,2-diphenylpyrazolidine (0.5 g.) in a mixture of ethanol (15 c.c.) and crushed ice (20 g.) was added to 2N hydrochloric acid (250 c.c.). A 2N solution of sodium nitrite (250 c.c.) was slowly added to the mixture, followed by water (250 c.c.), and the resultant solution allowed to stand for 24 hr. No solid separated out, and the solution was extracted with ether. On drying, and evaporating the ether extract to dryness, a red oil was obtained, from which no solid, other than azobenzene, could be isolated.

Attempted Reduction of 4-Hydroxy-4-hydroxylamino-3-nitrosoamino-5-oxo-1,2-diphenylpyrazolidine. - 4- Hydroxy-4-hydroxylamino-3-nitrosoamino-5-oxo-1,2-diphenylpyrazolidine (0.5 g.) was added slowly to a vigorously stirred mixture of concentrated hydrochloric acid (10 c.c.), ice (25 g.), and zinc dust (2 g.). The mixture was stirred for 4 hr., the temperature being allowed to rise to that of the room. The acid solution was then filtered free of excess zinc, and

poured into ammonia (0.88, 30 c.c.). No solid separated out, and the ammoniacal solution was thoroughly extracted with ether. The ether solution was evaporated to dryness giving a black oil, from which no solid, other than azobenzene, could be isolated.

4-Amino-3-imino-5-oxo-1,2-diphenylpyrazolidine. - 3-Imino-4-isonitroso-5-oxo-1,2-diphenylpyrazolidine (5 g.) was slowly added to a vigorously stirred mixture of concentrated hydrochloric acid (50 c.c.), ice (250 g.), and zinc dust (15 g.). The mixture was stirred for 1½ hr., filtered free from the excess of zinc, and added to ammonia (0.88 c.c.-70 c.c.). A pale yellow solid crystallised from the ammonia m.p. 167°. This was crystallised from chloroform-methanol as white needles of 4-amino-3-imino-5-oxo-1,2-diphenylpyrazolidine (4.5 g.), m.p. 167°, (Found: C,67.45; H,5.2; N,20.7. $C_{15}H_{14}N_4O$ requires C,67.65; H,5.3; N,21.0%), λ max. 206 (ε, 19,000) and 252 mμ (ε, 18,000); ν max. 3240, 3090 (NH) and 1688 $cm.^{-1}$ (C:O).

Condensation of 4-Amino-3-imino-5-oxo-1,2-diphenylpyrazolidine with Ethyl Chloroformate. - 4-Amino-3-imino-5-oxo-1,2-diphenylpyrazolidine (100 mg.) was dissolved in chloroform (30 c.c.), and ethyl chloroformate (1 c.c.) was added. The mixture was refluxed for 1 hr., the chloroform was then distilled off giving a white solid, which was

filtered off and crystallised as white plates of 4-carbethoxy-amino-3-imino-5-oxo-1,2-diphenylpyrazolidine (100 mg.), m.p. 250°, (Found: C, 63.41; H, 5.09; N, 16.28. $C_{18}H_{18}N_4O_3$ requires C, 63.89; H, 5.36; N, 16.56%), λ max. 206 (ε, 22,300) and 258 mμ (ε, 22,250); ν max. 3226 (NH) 1712 and 1678 $cm.^{-1}$ (carbonyl doublet).

Attempted Cyclisation of the Above Compound. -

(a) By Sublimation. 4-Carbethoxyamino-3-imino-5-oxo-1,2-diphenylpyrazolidine (25 mg.) was sublimed at 200° at high vacuum. The sublimate was identical with the starting material.

(b) Heating in a Sealed Tube. 4-Carbethoxyamino-3-imino-5-oxo-1,2-diphenylpyrazolidine (20 mg.) was dissolved in chloroform, and the solution heated to 200° in a sealed tube for 4 hr. On cooling, and concentrating the chloroform solution, the starting material (18.2 mg.) was recovered.

(c) Refluxing with Acetic Anhydride. - 4-Carbethoxyamino-3-imino-5-oxo-1,2-diphenylpyrazolidine (28 mg.) was refluxed for 4 hr. with an excess of acetic anhydride (10 c.c.). Water was then added, and the starting material (21.5 mg.) was recovered unchanged from the acetic acid.

Condensation of 4-Amino-3-imino-5-oxo-1,2-diphenyl-pyrazolidine with Nitrous Acid. - 4-Amino-3-imino-5-oxo-1,2-diphenylpyrazolidine (100 mg.) was dissolved in hot

2N hydrochloric acid (25 c.c.). The solution was cooled, and a solution of sodium nitrite (2N 25 c.c.) was added together with ice (25 g.) The red solid, which gradually separated, was filtered off, and crystallised from chloroform-methanol as red needles of 4-azo-3-imino-5-oxo-1,2-diphenylpyrazolidine (85 mg.), m.p. 130° (with detonation), (Found: N, 25.4: $C_{15}H_{12}N_5O$ requires N, 25.1%), λ max 206 (ε, 30,500), 234 (ε, 22,500) and 280 mμ (ε, 14,000); ν max. 2155 (azo) and 1724 $cm.^{-1}$ (C:O). The compound did not give a Beilstein test for halogen.

Condensation of 4-Amino-3-imino-5-oxo-1,2-diphenylpyrazolidine with Carbonyl Chloride. - 4-Amino-3-imino-5-oxo-1,2-diphenylpyrazolidine (250 mg.) in chloroform (50 c.c.) was treated with carbonyl chloride (5 c.c.). The resultant mixture was refluxed for 4 hr., when water was added to destroy the excess of carbonyl chloride. The chloroform layer was washed thoroughly with water, dried, and concentrated giving 4-carbethoxyamino-3-imino-5-oxo-1,2-diphenylpyrazolidine (50 mg.), m.p. and mixed m.p. with an authentic specimen 250°. No other product was isolated.

The above was repeated in ethanol-free chloroform using 4-amino-3-imino-5-oxo-1,2-diphenylpyrazolidine (250 mg.), and carbonyl chloride (5 c.c.). On treatment as above 4-carboxyamino-3-imino-5-oxo-1,2-diphenylpyrazolidine (40 mg.), m.p.

228-231° was isolated from the final chloroform solution, and purified by repeated precipitation from bicarbonate solution. (Found: C, 61.4; H, 4.3; N, 17.7. $C_{18}H_{14}N_4O_3$ requires C, 61.93; H, 4.52; N, 18.06%), λ max. 212 (ε, 15,300) and 246 mμ (ε, 12,100); ν max. 1640, 1740 (C:O) and 1800 cm.$^{-1}$.

In a further condensation, carbonyl chloride (10 c.c.) was added to 4-amino-3-imino-5-oxo-1,2-diphenylpyrazolidine (500 mg.) in toluene (200 c.c.), and the mixture was refluxed for 7 hr. The toluene was then washed free of the excess of carbonyl chloride, dried, and evaporated giving 4-carboxyamino-3-imino-5-oxo-1,2-diphenylpyrazolidine (100 mg.), m.p. and mixed m.p. with an authentic specimen 229-231°.

Condensation of 4-Amino-3-imino-5-oxo-1,2-diphenyl-pyrazolidine with Glyoxal Monohydrate. - Glyoxal monohydrate (500 mg.) in water (50 c.c.) was added to 4-amino-3-imino-5-oxo-1,2-diphenylpyrazolidine (100 mg.) in ethanol (50 c.c.), and the mixture was refluxed for 1 hr. On concentrating the solution, yellow needles of 5-oxo-1,2-diphenyl-3,4-pyrazino-pyrazolidine (30 mg.), m.p. 137° were obtained, (Found: C, 70.82; H, 4.13; N, 19.97. $C_{17}H_{12}N_4O$ requires C, 70.8; H, 4.16; N, 19.45%), λ max. 205 (ε, 24,100) and 270 mμ (ε, 19,400); ν max. 1695 cm.$^{-1}$ (C:O).

Condensation of 4-Amino-3-imino-5-oxo-1,2-diphenyl-pyrazolidine with Chloracetyl Chloride. - Chloracetyl chloride (2 c.c.) was slowly added to a stirred ice-cooled solution of 4-amino-3-imino-5-oxo-1,2-diphenylpyrazolidine (250 mg.) in chloroform-pyridine (20 c.c.-5 c.c.), and the mixture was allowed to stand for 2 hr. The chloroform solution was then washed successively with 2N hydrochloric acid, 2N sodium hydroxide solution and water, dried, and concentrated giving white crystals of 4-chloroacetylamino-3-imino-5-oxo-1,2-diphenylpyrazolidine (60 mg.), m.p. 238° recrystallised from chloroform-methanol as white needles, m.p. 238°. The compound gave a positive Beilstein test for halogen. (Found: C, 59.6; H, 4.22; N, 15.87. $C_{17}H_{15}ClN_4O_2$ requires C, 59.56; H, 4.38; N, 16.34%), λ max. 206 (ε, 24,200) and 257 mμ (ε, 25,200); νmax. 3175 (NH) or (OH) and 1613, 1681 cm.$^{-1}$ (both C:O).

Attempted Cyclisation of the Above Compound. - A solution of 4-chloroacetylamino-3-imino-5-oxo-1,2-diphenyl-pyrazolidine (100 mg.) in toluene (100 c.c.) was refluxed for 7 hr. with collidine (20 c.c.). The toluene was then washed free of collidine using 2N hydrochloric acid, and water, dried, and evaporated off. A trace of yellow gum was isolated, and this on treatment with petroleum ether (b.p. 40-60°) gave a yellow solid (4 mg.), m.p. 85-90°. This

compound showed λ max. 204 (ε, 19,000) 267 (ε, 8200) and 320 mμ (ε, 5600); ν max. 1690 cm.$^{-1}$ (C:O). Insufficient material was obtained for crystallisation to analytical purity even on repetition of the cyclisation.

Self-condensation of 4-Amino-3-imino-5-oxo-1,2-diphenylpyrazolidine. - It was noticed that on standing 4-amino-3-imino-5-oxo-1,2-diphenylpyrazolidine became yellow and on crystallisation a new substance was isolated, m.p. 189-190°. This product (120 mg.) was also obtained when a solution of 4-amino-3-imino-5-oxo-1,2-diphenyl-pyrazolidine (200 mg.) in ethanol (50 c.c.) was refluxed with platinum catalyst (trace). It was assigned the formulation 2,3-5,6-di-(5-oxo-1,2-diphenylpyrazolidine-3,4-pyrazine, (Found: C,72.42; H,4.1; N,16.4. $C_{30}H_{20}N_8O_2$ requires C,72.58; H,4.03; N,16.68%), λ max. 209 (ε, 36,100) and 232 mμ (ε, 31,800); ν max. 3280 (OH or NH) and 1667 cm.$^{-1}$ (C:O). Molecular weight found 480; required 490.

Condensation of 4-Amino-3-imino-5-oxo-1,2-diphenyl pyrazolidine with Acetylacetone. - 4-Amino-3-imino-5-oxo-1,2-diphenylpyrazolidine (100 mg.), and acetylacetone (5 c.c.) were refluxed for 1 hr. in ethanol (25 c.c.). Water was then added, and the mixture was allowed to cool. White needles of 4-acetylacetonamino-3-imino-5-oxo-1,2-diphenyl pyrazolidine (25 mg.), m.p. 238-239° were obtained. (Found:

C, 69.19; H, 5.53. $C_{20}H_{20}N_4O_2$ requires C, 68.9; H, 5.75%), λ max. 206 (ε, 29,000), 262 (ε, 26,500) and 308 mμ (ε, 23,000); ν max. 3310 (NH or OH), and 1626, 1681 $cm.^{-1}$ (C:O doublet).

Attempted Cyclisation of the Above Compound. -

(a) Using Acetic Anhydride. 4-Acetylacetonamino-3-imino-5-oxo-1,2-diphenylpyrazolidine (0.5 g.) was refluxed for 4 hr. in an excess of acetic anhydride (20 c.c.). Water was added and the solution was concentrated by distillation under reduced pressure. A red oil was obtained, from which no solid could be isolated. On standing for several days, azobenzene (100 mg.) m.p. 67° was obtained.

(b) Using Sodium Ethoxide. - 4-Acetylacetonamino-3-imino-5-oxo-1,2-diphenylpyrazolidine (0.45 g.) was refluxed for 4 hr. with sodium (0.5 g.) in ethanol (20 c.c.). Water was then added, and the solution was thoroughly extracted with ether. On drying, and distilling off the ether, a dark red oil was obtained, from which no solid could be isolated. Extraction of the acidified basic phase gave a trace of red-brown oil from which no solid could be isolated.

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PART II

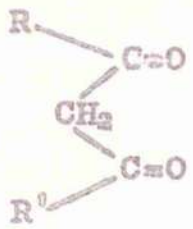
STUDIES IN THE METAL CHELATE FIELD

INTRODUCTION

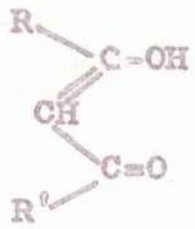
PART II

Although various metal derivatives of β-keto esters and β-diketones had long been known, their cyclic character was first postulated by Werner in 1901[1]. The term chelate, proposed by Morgan[2] to designate the cyclic unions of metal atoms with organic molecules, is derived from the Greek word 'chela' meaning the claw of a lobster or other crustacean.

The β-dicarbonyl compounds (I) form metal derivatives by virtue of their ability to enolise (II), the acidic hydrogen being replaced by the metal, which then co-ordinates to the carbonyl oxygen (III).



(I)



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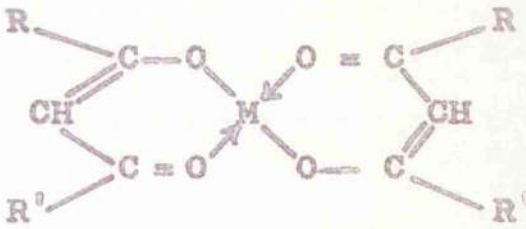
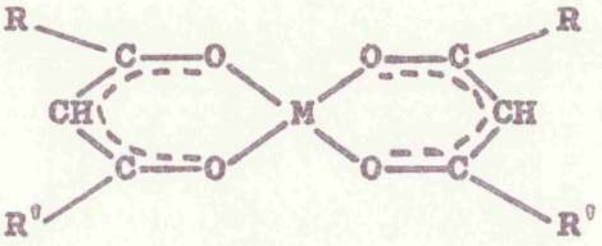


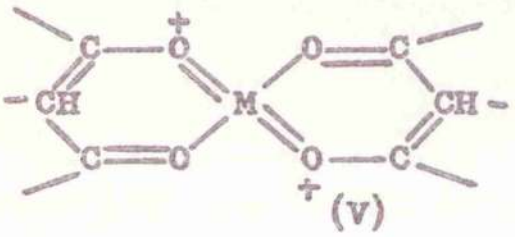
(III)

A great amount of consistent evidence has been built up proving the cyclic nature of chelate compounds, and this is discussed fully by Diehl[3] in a review. However, the simple cyclic formation postulated by Werner does not explain the great stability of the metal chelate compounds. The acetylacetonates of several metals can be distilled without decomposition at temperatures up to 300°.[2] The more modern concept is one of resonance stabilisation with delocalisation of the double bonds in the chelate ring, giving it a 'pseudo-aromatic' character (IV).

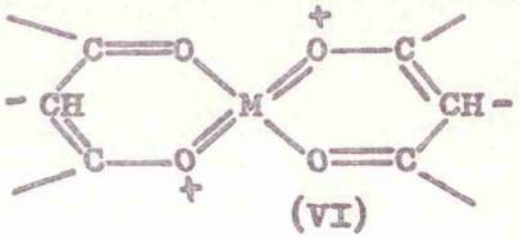


(IV)

This has been carried further by Martell and Calvin[4] who propose resonance contributions of structures (V) and (VI) for transition metal chelates.



(V)



(VI)

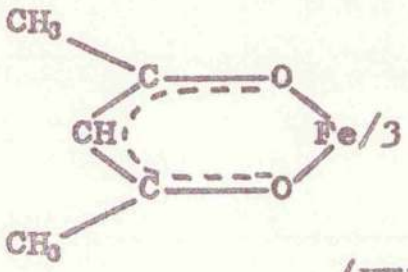
The ions of transition metals, which are most easily introduced into chelate compounds, have vacant low-energy orbitals which are capable of accepting electron pairs to form homopolar bonds. It is fairly well established that the order of divalent metal complexes of organic ligands is as follows:-

Pd > Cu > Ni > Pb > Co > Zn > Cd > Fe > Mn > Mg.

and this is the order of increasing basicity, and applies irrespective of ligand.[5,6] Hence the tendency for chelation can be related to the tendency for the above metals to form homopolar bonds, which must, according to Calvin, involve d orbitals of the metals.[7]

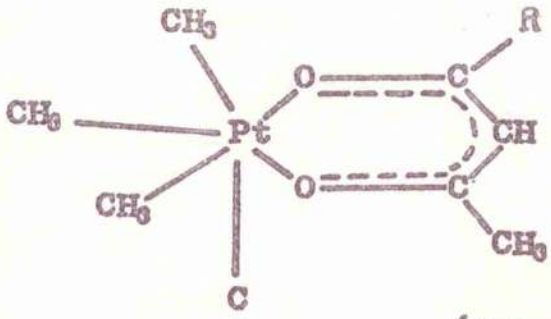
However, recent X-ray evidence for ferric acetylacetonate[8] (VII) indicates that the metal-oxygen bond is too long to have any double-bond character, but that the carbon-carbon

and carbon-oxygen distances in the chelate ring have both double and single bond character in agreement with a pseudo-aromatic structure.



(VII)

Other X-ray evidence for the structures of trimethyl platinum ethyl acetoacetate[9] (VIII, R = OEt), and trimethyl platinum acetylacetonate[10] (VIII, R = CH_3) also shows that the average platinum-oxygen bond length is significantly longer than the expected single-bond value, thus appearing to rule out double-bond character. In these compounds also, the carbon-carbon and carbon-oxygen bond lengths in the chelate ring are indicative of pseudo aromaticity.



(VIII)

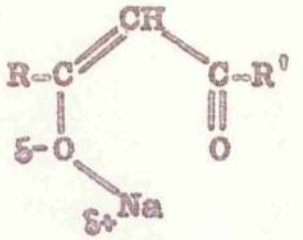
The problem of partial or complete delocalisation has still to be resolved.

The metal chelates of β-dicarbonyl compounds are generally non-electrolytes, being insoluble in water,

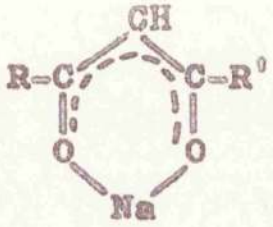
soluble in non-polar solvents, and having distinct melting points. The alkali metal chelates tend to be slowly dissociated by water.[3]

With the notable exception of the mercuric chelates, most of the metal chelates of the β-dicarbonyls have similar infrared absorption spectra, the region 1350 cm.$^{-1}$ to 1600 cm.$^{-1}$, the 'chelate carbonyl' region,[11,12] being particularly characteristic. The ultraviolet absorption spectra of metal chelates have been correlated with the type of bonding present in the chelate,[13,14] at least in a qualitative way. It was observed that ionic chelates had similar absorption spectra to the chelating agent, whereas in covalent chelates although the same absorption peaks are present in the ultraviolet, these peaks are shifted to longer wave-lengths. The greater the covalency of the bonding of the chelate, the greater is this shift.

The alkali and alkali earth metal complexes of β-dicarbonyl compounds have been studied by Sidgwick and Brewer,[15] who subdivided such complexes into two classes, salts (IX), and 2-covalent complexes (X), the latter having distinct melting points, and being soluble in non-polar solvents.

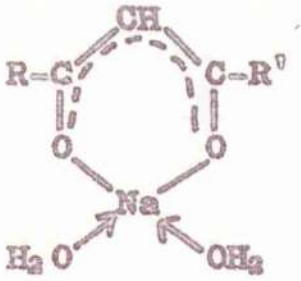


(IX)



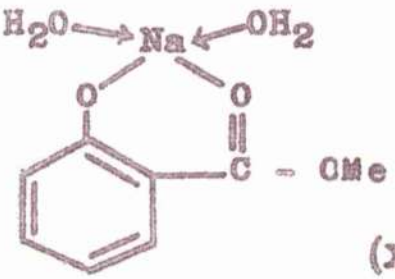
(X)

However, many 4- and 6-covalent alkali and alkaline earth metal derivatives of β-dicarbonyl compounds have been isolated. The sodium derivative of benzoylacetone is by definition a salt, but its dihydrate (XI, R = Ph, R' = CH_3) has a distinct melting point and is relatively soluble in non-polar solvents.[15]



(XI)

The corresponding lithium derivative can be obtained, and there are several other instances of this type of conversion of salts to covalent complexes, for example the hydrates of the sodium salts of ethyl acetoacetate (XI, R = CH_3, R' = OEt), acetylacetone (XI, R = R' = CH_3), and methyl salicylate (XII), are all 4-covalent complexes.



(XII)

Similarly, many sodium derivatives of β-dicarbonyl compounds, normally insoluble in non-polar solvents, dissolve in the presence of an excess of the parent or other dicarbonyl compound, or if water or any other polar substance is added.[25]

The formation of 4-covalent complexes of the alkali and alkali earth metals by solvation of the salts with alcohols, or alkyl or acyl halides would be extremely difficult to establish because of the low stability of such compounds. However, Brändström[26] believes that the formation of 4-covalent complexes of the latter type is the initial step in alkylation and acylation reactions of β-dicarbonyl complexes.

Structures of the Transition Metal Chelates.

The bonds between a metal ion and a given donor atom or atoms in a complex are either ionic, or covalent, or of some intermediate character. As yet the concepts of the metal-donor linkage are in the formulative stage, and no complete theory has been devised. The measurements of magnetic susceptibility have been most useful in determining bond type in metal chelates, if only for a limited range of metals. The magnetic susceptibility for the ions of the first transition series is a function of the number of vacant d orbitals. Such ions may accept electrons from a

donor in one of two ways. If the combination is purely ionic and the central ion retains its charge, then its magnetic susceptibility is unchanged by chelate formation. Conversely, if the donor forms a covalent bond with the metal, the electron pair of the donor must occupy one of the available orbitals in the metal. Since the magnetic dipole moment is dependent on the number of available orbitals, covalent bonding may greatly alter the magnetic susceptibility.

COPPER

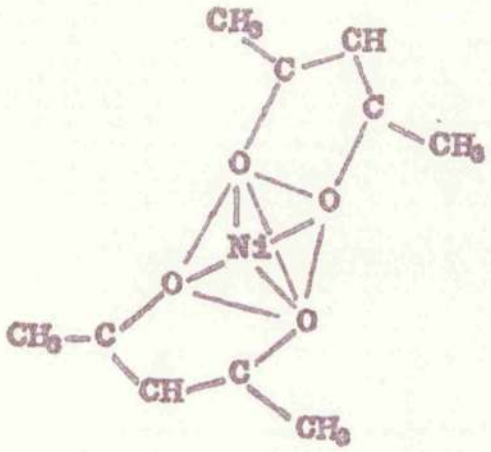
Unfortunately, the magnetic criterion is not applicable to copper chelates, since all three possible bond configurations, tetrahedral-ionic, planar (dsp^2)-covalent, and tetrahedral (sp^3)-covalent, involve one unpaired electron and are therefore indistinguishable. However, it is generally accepted that covalent bonds are directed in space, while primarily ionic bonds are not. This means that 4 ionic bonds will arrange themselves tetrahedrally and six ionic bonds will be arranged octahedrally, if free to do so. Hence a square-planar arrangement of 4 bonds can be taken to comprise a covalent structure.

Cox and Webster[17] in an X-ray crystallographic study, established the square-planar configuration of the copper chelates of acetylacetone, benzoylacetone, dipropionylmethane, and 3-chloroacetylacetone, thus indicating a high

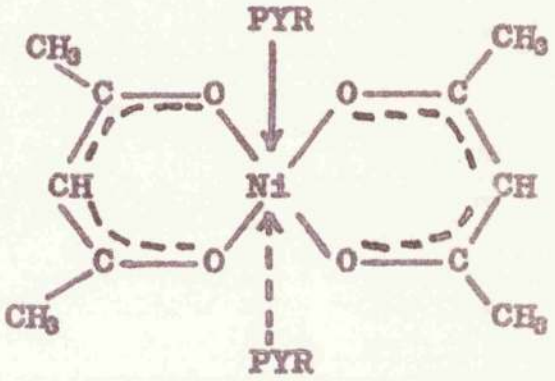
degree of covalence in the copper dicarbonyl chelates. A further point in the structure of copper chelates must be made at this time. Although it is generally accepted that copper has a maximum co-ordination number of four in its derivatives, several instances have been recorded of the formation of a weak fifth co-ordinate bond. For example the copper derivatives of glycine, and alanine[18] co-ordinate a further molecule of the amino-acid, the copper derivative of ethylenediamine also co-ordinates further with an excess of the amine,[19] and more relevantly, copper acetylacetonate forms a green additive with quinoline,[20] making the copper pentaco-ordinate in each case.

NICKEL

From measurements of magnetic susceptibilities, Mellor and Craig[21] deduced that all nickel complexes, in which the nickel is co-ordinated to four oxygen atoms, are paramagnetic and ionic in type, with considerable deviation of bond angles from the planar structure. Such nickel complexes readily take two additional donors to form octahedral complexes, in which the nickel has its maximum covalency of six. For example, paramagnetic bis-acetylacetone nickel (XIII), is readily converted to a bis-pyridine octahedral structure (XIV).[22]



(XIII)



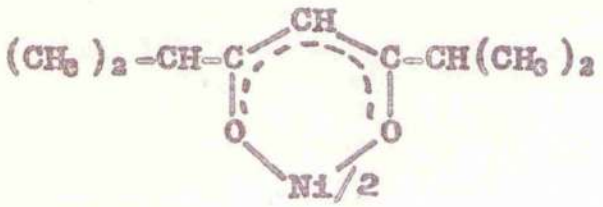
(XIV)

Many other such pyridine solvates of nickel chelates of β-dicarbonyl compounds are known, and are very stable.[23]

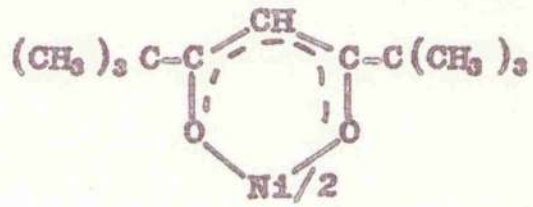
In contrast to this, diamagnetic nickel chelates, for example nickel dimethyl glyoxime, do not solvate readily, and the nickel cannot be exchanged with labelled nickel in ion-exchange experiments.[24] This indicates the covalency of the bonding in such structures. However, even the diamagnetic chelates can be solvated in strong co-ordinating solvents, showing magnetic moments corresponding to up to two unpaired electrons in these solvents, thus indicating that the transition from ionic to covalent structures is readily obtained, depending on the solvent used.

Further evidence for this ready interconversion is given by Cotton in a recent paper.[25] In the diketone series, nickel di-isobutyroylmethane (XV), in non-solvating media, has a magnetic moment which depends on concentration

and temperature, with a colour change from green to red occurring at 50°. The magnetic moment of nickel acetylacetone shows similar dependence in non-polar solvents, with a similar colour change at 200°. Nickel dipivaloylmethane (XVI) forms red solutions with non-solvating media at room temperature[26] but green solutions in solvents such as pyridine and ethylene glycol dimethyl ether.



(XV)



(XVI)

The ultraviolet absorption spectra of nickel chelates of β-dicarbonyl compounds have been used by McKenzie and co-workers[13] to distinguish ionic from covalent chelates. They found that ionic chelates had absorption spectra similar to those of the β-dicarbonyl compound, whereas covalent chelates showed strong absorption bands characteristic of the chelate.

ZINC.

Unlike copper and nickel, zinc is unable to increase its co-ordination number above four, that required for chelation. Of the metals in the first transition series, zinc is the only one unable to form either square dsp^2 or

octahedral d^2sp^3 bonds due to the absence of available d orbitals for bonding. This means that the bonds formed by zinc in its complexes are predominantly ionic and consequently tetrahedral. This explains why, in the series Mn, Fe, Co, Ni, Cu, the stability of the metal complexes increases from Mn to Cu and then falls off with zinc, irrespective of organic ligand.[18]

However, it is worthy of note that zinc chelates have higher stability constants, on a basis of the ratio of charge to ionic radius, than the corresponding complexes of the alkali earth metals, indicating, in all probability, a greater degree of covalency in the bonding of the zinc chelates.[27]

MERCURY.

Like zinc, mercury has a maximum covalency of four, that required for chelation, and is therefore unable to co-ordinate further. However, the fact that the mercury complexes of the β-dicarbonyl compounds show normal carbonyl frequency in the infrared spectra[25] suggests that these complexes are not chelates, but acyclic salts. To date the problem of the structure of the mercury complexes has not been resolved.

Stability of Chelates.

(a) Diketone Acidity. It is already obvious that variation of the metal ion in a chelate can greatly alter the stability of the chelate. Many other factors, such as steric requirements and electronic influences in the organic ligand, may also affect the stability and hence the reactivity of chelates. In a series of papers[28-31] Fernelius and co-workers correlated the acid strength of β-dicarbonyl compounds with the stability of the metal chelates formed from them. However, in their correlation, an average value of Kf1 and Kf2 was taken to represent the chelate stability, where Kf1 and Kf2 are the formation constants for the first and second steps in the formation of a bivalent metal chelate, according to the equations:-

$$M^{++} + CH^{-} \rightleftharpoons M.Ch^{+} \qquad Kf1 = \frac{[M.Ch^{+}]}{[M^{++}][Ch^{-}]}$$

$$M.Ch^{+} + Ch^{-} \rightleftharpoons M.Ch_2 \qquad Kf2 = \frac{[M.Ch_2]}{[M.Ch^{+}][Ch^{-}]}$$

A truer concept of the stability constant K can be obtained from the product of Kf1 and Kf2, giving:-

$$K = \frac{[MCh_2]}{[M^{++}][Ch^{-}]^2}$$

However, from the correlation it was deduced that the logarithm of the average value of the formation constants,

Kf1 and Kf2, (Kf_{av}) is a linear function of the negative logarithm of the acid dissociation constant, (PK_d) of the β-dicarbonyl compound. Further, it is observed that β-diketones having two aromatic rings as end-groups, for example dibenzoylmethane (XVII, R = R' = Ph), form more stable chelates than β-diketones of comparable acid dissociation constants, having two alkyl end-groups, for example, acetylacetone (XVII, R = R' = Me).

$$R.CO.CH_2.CO.R'$$

(XVII)

A summary of the more relevant results is presented in Table I, from which it can be seen, that as the acidity of the diketone rises (PKd falls), the stability of the chelate decreases (Log Kf_{av} falls) in a regular trend.

TABLE I

Diketone	PK_d	Log Kf_{av}.		
		Cu	Ni	Ba
D.B.M.	13.75	12.5	10.09	5.7
B.A.	12.85	11.51	9.0	4.7
A.A.	12.7	11.3	8.69	4.5
T.F.A.A	8.7	8.6	7.1	4.4

D.B.M.-dibenzoylmethane, B.A.-benzoylacetone, A.A.-acetyl acetone, T.F.A.A.-trifluoroacetylacetone, (XVII, R=Me, $R' = CF_3$).

However, corresponding figures obtained by the same workers[32,33], but using K = Kf1 x Kf2 are given in Table II. As can be seen, the values thus obtained are much closer to one another than those in Table 1 and no trend in stability with acid strength is discernible.

TABLE II

Diketone	Pkd	Log Kf1 x Kf2	
		Cu	Ni
D.B.M.	13.75	18.1	13.28
B.A.	12.85	18.1	13.02
A.A.	12.7	18.2	12.98
T.F.A.A.	8.7	12.7	10.0

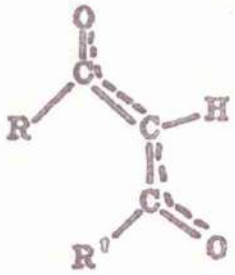
Abbreviations as in Table I

It would be expected that a decrease in the acidity of a diketone, that is, an increase in the basicity, will make the carbonyl oxygen atoms more negative, hence giving stabler chelates. However, many other factors can and do affect chelate stability as will be seen later.

(b) Steric Factors. In a recent paper,[34] Hammond and co-workers discussed an investigation of the effect of steric changes in β-diketones, on the acid dissociation constants. The results are shown in Table III.

TABLE III	
Diketone	-Log Acid Dissociation Quotient.
Acetylacetone	11.27
Di-isobutyroylmethane	12.48
Di-pivaloylmethane	14.48

It can be seen that the acidity of the diketone is reduced markedly as the size of the aliphatic end-group is increased. This is explained by an inhibition of the trans enolate anion (XVIII) by steric interference between the bulky end-groups. This effect is greater than the one expected from the acid-weakening inductive effect of the methyl groups.



(XVIII)

This steric inhibition causes the phenyl group in dibenzoylmethane to have an acid-weakening effect, compared with acetylacetone, whereas in benzoic acid the same group is acid-strengthening, compared with acetic acid. In a further study,[35] Hammond and co-workers showed that this steric effect also influenced the stability of the chelates formed from the above diketones. They stated that large

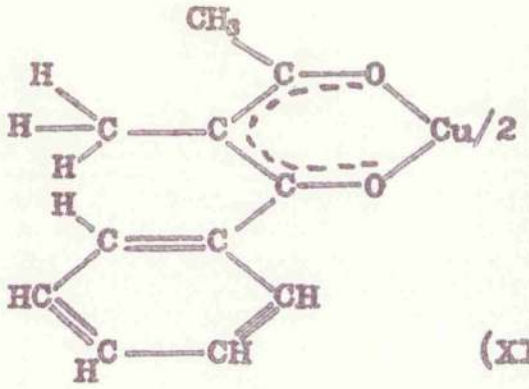
end-groups, for example, isopropyl, or t-butyl, will force the carbonyl oxygens together, thus increasing the basicity of the ligand, with consequent increase in the chelate stability, as can be seen in Table IV.

TABLE IV

Diketone	Cu Kf1	Kf2	Ni Kf1	Kf2
Acetylacetone	11.57	9.64	8.24	6.39
Di-isobutyroylmethane	12.29	9.99	8.73	7.58
Di-pivaloylmethane	13.91	11.55	9.9	9.1

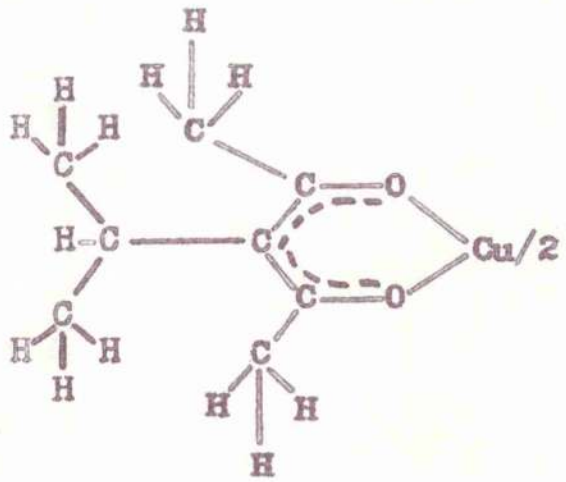
The effect of the phenyl group is not considered, although Hammond states that the sterically hindered dibenzoylmethide ion has a much smaller affinity for the sodium ion than the acetylacetone ion, indicating that dibenzoylmethane forms less stable chelates than acetylacetone. This is opposite to the effect observed by Fernelius.[29]

A further steric effect on chelate stability is observed in 3-substituted β-diketone complexes. 3-Methyl benzoylacetone copper chelate (XIX) has a much lower stability constant than might be expected on a basis of acid strength. This is a result of steric interference between the 3-methyl group and the phenyl ring, causing a distortion of the planar chelate ring with subsequent reduction in resonance stabilisation energy.[24]



(XIX)

Similarly, Morgan[37,38] found that acetylacetonates substituted in the 3-position with an isopropyl (XX) or sec.butyl group, did not give the usual coloured copper chelates, whereas the 3-isobutyl derivative (XXI), in which a methylene group is interposed between the chelate ring and the isopropyl group, is sufficiently free from steric interference to form a normal copper chelate.



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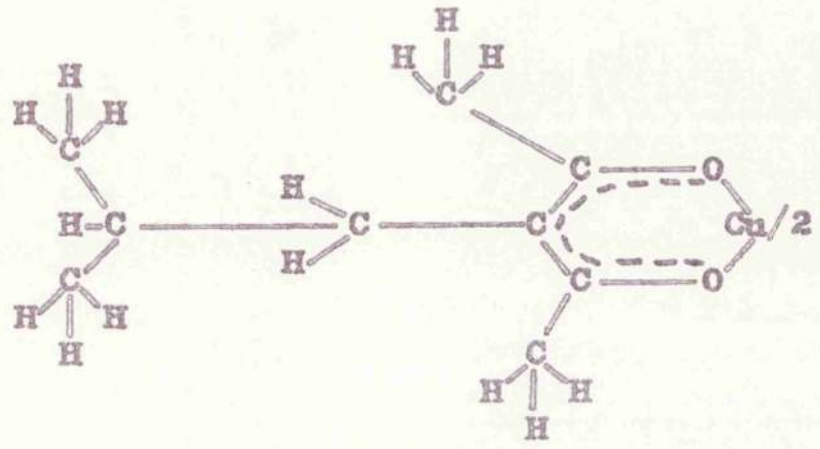


(XXI)

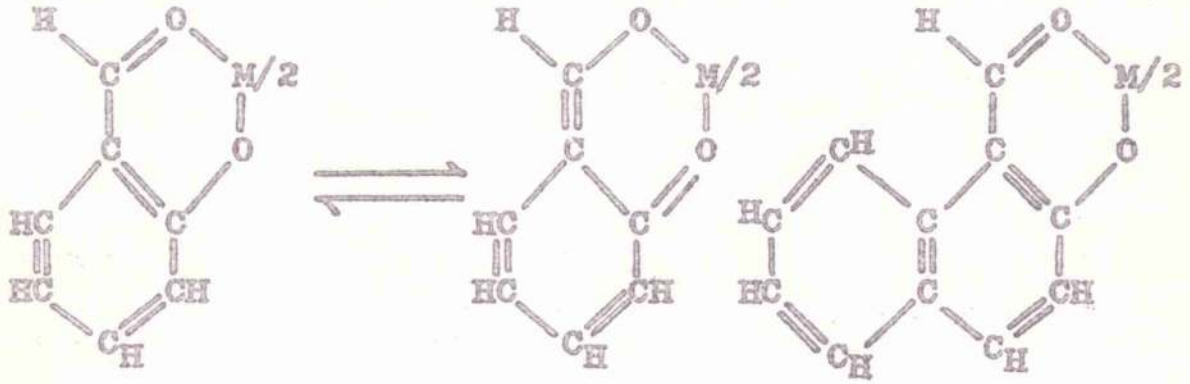
(c) Electronic Factors. The electronic effects associated with the chelate substituents can be subdivided into the inductive and mesomeric effects. The inductive effect of the substituent can be expected to influence the negativity of the adjacent carbonyl oxygen, as it influences the negativity of the oxygen atom in the simple aliphatic or aromatic acid series. This means, that aliphatic substituents will increase the negativity of the oxygen atom of the adjacent carbonyl group in the order $CH_3-\langle$ $(CH_3)_2CH-\langle$ $(CH_3)_3C-$, and that a phenyl substituent will decrease the negativity of the adjacent carbonyl oxygen.

An illustration of the mesomeric effect can be obtained from a comparison of the copper chelates of ethyl acetoacetate and acetylacetone. The former compound is considerably less stable and this is taken to be due to

participation of the strong ester resonance (XXII)[39] which, although it increases the basicity of the oxygen atom, interferes with the resonance of the chelate ring, with a resultant decrease in chelate stability.

(XXII)

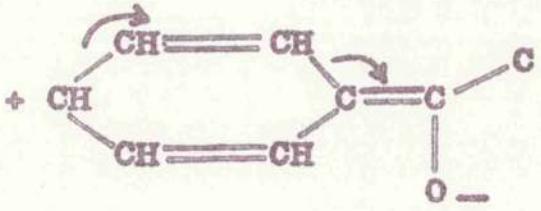
Similar reductions in chelate stability are observed in systems with 'crossed resonance', for example, salicylaldehyde (XXIII) and 2-hydroxy-1-naphthaldehyde (XXIV) chelates.[39] In these, the double bond in the chelate ring has to participate in both aromatic and chelate resonance with resulting decrease in chelate stability, from the value expected on a basis of acid strength.



(XXIII) (XXIV)

Hence it might be expected that any resonance effect associated with phenyl substituents in the diketone (XXV)

would have an adverse effect on chelate stability.



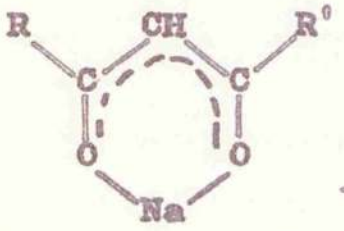
(XXV)

Summarising the effects of variations of the β-diketone substituents on the stability of the corresponding metal chelates, it can be seen that substitution of a group on the diketone may affect the tendency for chelation in several ways. It may influence the acidity of the diketone, or it may interfere with or enhance the resonance stabilisation of the chelate ring. Further, the addition of groups to the diketone may, by purely steric interaction, prevent the diketone from assuming the configuration most suitable for chelation to the metal ion.

Reactions of Chelates of β-Dicarbonyl Compounds.

(a) Alkali Metal Chelates. Sodium 'salts' of β-dicarbonyl compounds have long been used as intermediates in the synthesis of alkyl and acyl derivatives of the dicarbonyl compounds,[41-45] substitution occurring mainly at the central carbon atom to give compounds of general formula (XXVI). However, in the reaction of a β-dicarbonyl complex, two

possible products can be formed. These are, a substituted dicarbonyl compound (C-substituted product) (XXVI) and an enolic ester or ether of the dicarbonyl compound (O-substituted product) (XXVIII), formed by reaction at the central carbon atom or the carbonyl oxygen atom respectively.



$R''X$

$R.CO.\underset{\underset{R''}{|}}{CH}.CO.R'$ (XXVI) and/or

$R.\underset{\underset{O.R''}{|}}{C}=CH.CO.R'$ (XXVII)

R'' is alkyl, aryl, acyl, allyl.

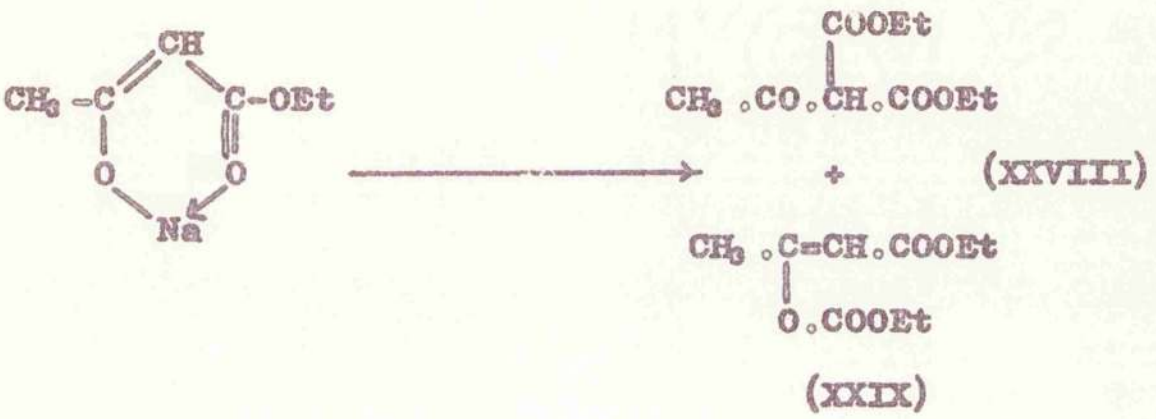
In this connection, Brändström has reviewed the literature relating to the alkylation and acylation of alkali metal complexes of β-dicarbonyl compounds under conditions which lead to extensive (or complete) complexing of the enolate anions, by the metal ions.[16] It is worthy of note that in many of the reactions described, the alkali metal complex as such was never isolated, but was formed in situ, normally by dissolving the alkali metal in an ethanolic solution of the β-dicarbonyl compound.[41-44] This would appear to be a reaction of the enolate anion rather than the metal complex.

Many such reactions of the alkali metal chelates have been carried out, with a variety of alkylating agents, and

in solvents such as ether,[46] benzene,[46] ethanol,[44,47,48,52] dioxan,[49,50,52] toluene,[51,52] and dimethylformamide.[48] However, since the primary object of the reactions was the preparation of the C-substituted product, details of the isolation and identification of any O-substituted product were neglected and the work is therefore of limited importance for providing an indication of the factors influencing the ratio of C- to O-substitution.

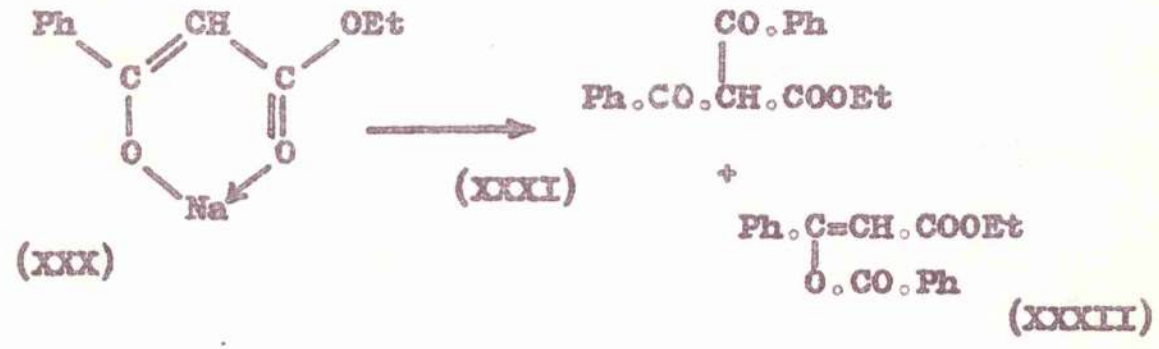
Relatively fewer reactions involving acylating agents have been instanced in the literature, and these also were primarily concerned with the synthesis of the C-acylated products.[53-58] However, some mention has been made of the isolation and identification of O-acylated derivatives from reactions of alkali metal complexes of β-dicarbonyl compounds with acylating agents, in ether.[59,60]

It is interesting to note that some indication of the effect of solvent on the direction of the reaction can be abstracted from the literature. The reaction of ethyl chloroformate with sodium ethyl acetoacetate has been investigated by several workers under different experimental conditions. Michael[61] and Claisen[62] concluded that the reaction in ether gave both C- (XXVIII) and O-substitution (XXIX), the latter predominating.



The same reaction carried out in ethanol gave the C-substituted product, diethyl acetylmalonate (XXVIII) in almost quantitative yield.[63,64]

A further indication can be obtained by examination of the reaction of sodium ethyl benzoylacetate (XXX) with benzoyl chloride. In ether,[59] the reaction yielded both the C- (XXXI) and the O- (XXXII) acyl products in the ratio 2:1.



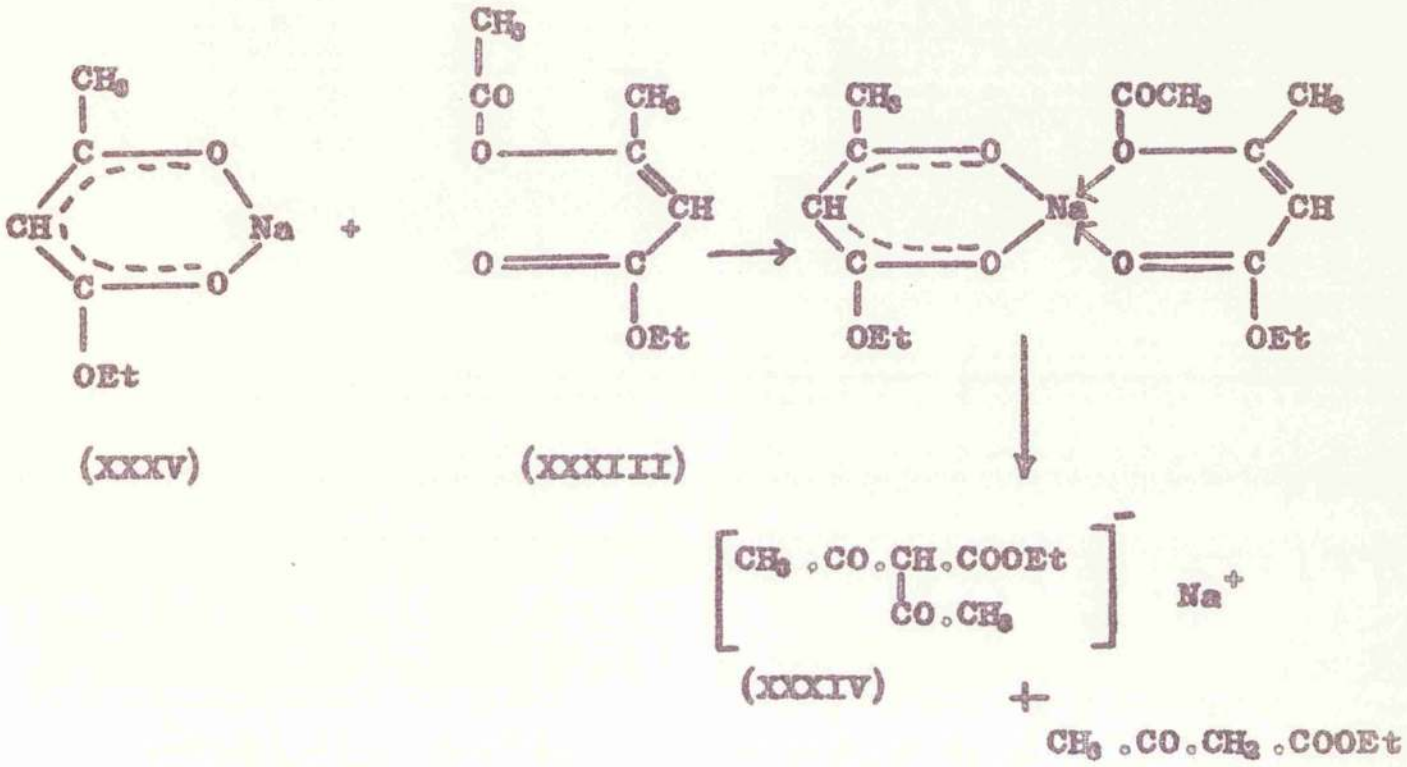
In ethanol, the C-acyl derivative was isolated in a state of analytical purity as the sole product of reaction.[42]

Although limited in extent, the above comparisons indicate that some measure of control of the reaction path is

afforded by variation of the reaction media. It would appear that the reactions of sodium complexes of β-dicarbonyl compounds with alkylating and acylating agents give a higher percentage of C-substitution in polar solvents than in non-polar solvents.

Mechanism of Reaction of the Alkali Metal Complexes.

Many hypotheses have been made as to the mechanism of the reaction of alkali metal chelates of β-dicarbonyl compounds with alkylating and acylating agents. Claisen[85] believed that C-substitution occurred as a secondary process, by isomerism of the O-substituted product. This hypothesis was substantiated by the facile base-catalysed isomerism of ethyl O-acetylacetoacetate (XXXIII) to ethyl C-acetyl-acetoacetate (XXXIV), the latter being isolated as its sodium salt.[86] One of the catalysts used for this isomerism was sodium ethyl acetoacetate (XXXV), and the mechanism has been considered as a C-acylation of the catalyst, the ethyl O-acetylacetoacetate acting as the acylating agent.

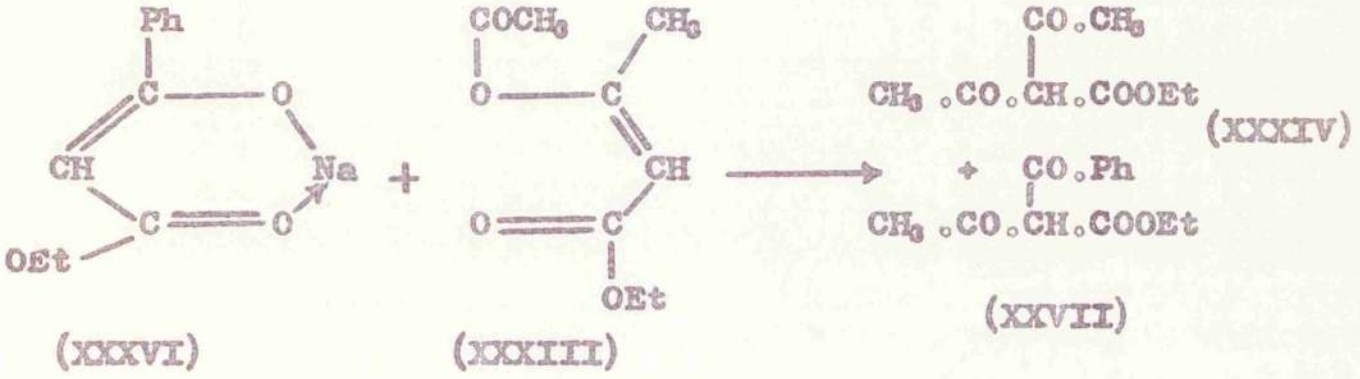


(XXXV) (XXXIII)

(XXXIV)

$CH_3 \cdot CO \cdot CH_2 \cdot COOEt$

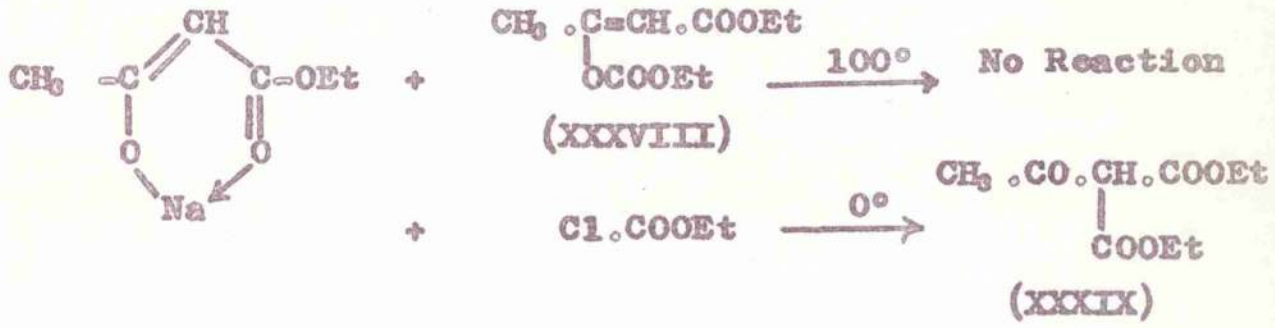
However, although this established the mechanism of O- to C- isomerism, it did not prove that the C-substitution was a secondary reaction following initial O-substitution.



(XXXVI) (XXXIII) (XXXIV) (XXVII)

Michael[55] finally showed that, under conditions in which sodium ethyl acetoacetate failed to effect the isomerism of ethyl O-acetylacetoacetate,[68] acetyl chloride reacts with sodium acetoacetate to give ethyl C-acetylacetoacetate as the main product.

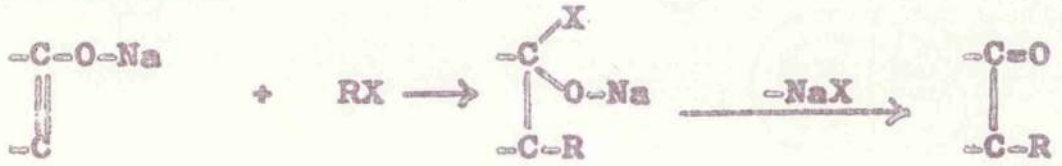
Further, although treatment of ethyl O-carbethoxyaceto-acetate (XXXVIII) with sodium ethyl acetoacetate at 100° for 10 hr. failed to give any diethyl acetyl malonate (XXXIX),[16] this product was isolated in almost quantitative yield by the action of ethyl chloroformate on sodium ethyl acetoacetate at 0°.[64,65]



(XXXVIII) (XXXIX)

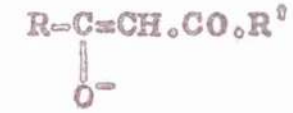
Having shown that the formation of the C-substituted product is a primary reaction, Michael[55] proposed that C-alkylation

was due to addition of the alkylating agent to the double bond of the enolate, followed by liberation of the alkali metal halide.



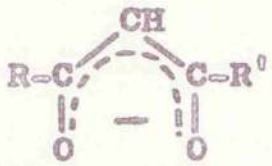
However, this was refuted by the incapacity of the alkyl halides under the reaction conditions to alkylate the keto-enols by addition to the double bonds.[60]

Later, Arndt[70] and other workers developed the concept of an ionic reaction of the alkali metal chelates of tautomeric substances. By this, reaction was believed to take place through the anion of the tautomer, the negative charge being localised on the carbonyl oxygen or the central carbon atom. Substitution could then occur by attack at either of these two positions, dependent on the nature of the attacking reagent and the reaction conditions, giving C- or O- substitution or a mixture of both. The main criticism of this concept was derived from spectral evidence, which indicated that the anions of the alkali metal chelates of β-dicarbonyl compounds have an enolic structure (XL) similar to the corresponding O-substituted derivatives, and with the charge on the carbonyl oxygen atom.[69]



(XL)

It soon became apparent that this concept, although correct in part, was not complete, and it was developed further. Kornblum and co-workers[71] postulated the existence of a mesomeric anion (ambident anion), in which neither the double bonds, nor the charge are localised (XLI).



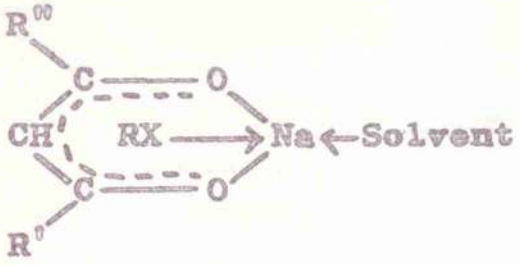
(XLI)

This anion is postulated as being formed in the transition state of the reaction, this transition state having both S_N1 and S_N2 character, the balance of which being determined both by the nature of the attacking group, and by the reaction conditions. Both C- and O-substitution are envisaged as occurring by the same mechanism, through the same reaction intermediate. The greater the S_N2 character in the transition state the greater will be the preference for covalency formation with the atom of lowest negativity in the mesomeric anion, that is the central carbon atom.

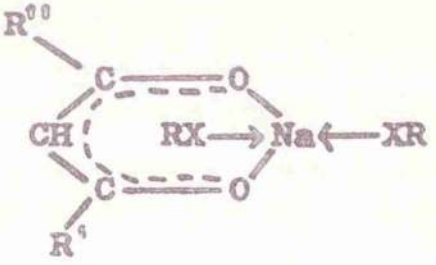
Conversely, the greater the S_N1 character in the transition state, the greater will be the preference for bond formation with the atom of highest electronegativity in the anion, that is, the carbonyl oxygen atom.

Brändström,[16] while agreeing with the concept of the mesomeric anion, further postulated a specific mechanism for

C-substitution. He put forward the theory that a co-ordination of the halogen of the attacking group to the alkali metal of the complex is the initial step in the reaction of acylating and alkylating agents with alkali metal complexes of β-diketones. In polar solvents, for example ethanol, this co-ordination will result in the formation of a 4-covalent alkali metal complex (XLII), and in non-polar solvents, such as ether and benzene, a complex of type (XLIII) will be formed.



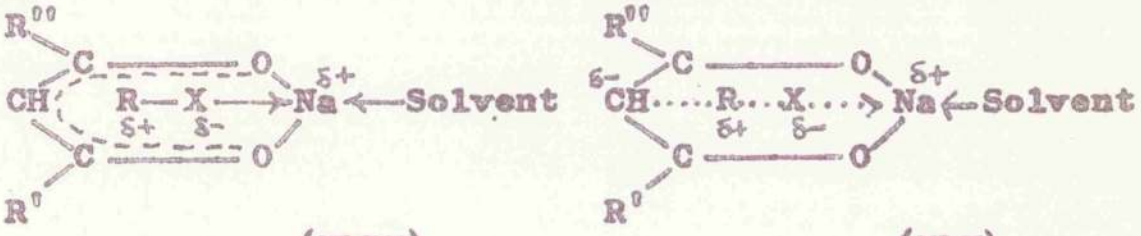
(XLII)



(XLIII)

This initial co-ordination of the halogen to the alkali metal will increase the polarisation of the halogen-carbon bond in the attacking group, giving the alkyl or acyl group R a resultant partial positive charge, (XLIV). This charge, in turn, will be attracted to the π-electrons in the chelate ring, and from strain and sterical considerations will favour interaction with the central carbon atom, as this enables formation of a transition state having a strainless six-membered ring (XLV), thus stabilising the mesomeric form

of the anion with the charge on the carbon atom.



(XLIV) (XLV)

Brändström postulates that no similar interaction at the carbonyl oxygen atoms will occur, as this will give rise to a strained 4-membered ring in the transition state. Hence stabilisation of the mesomeric form of the anion with the charge on the central carbon atom is taken to account for the high proportion of C- to O- substitution in the reactions of alkali metal complexes of β-dicarbonyl compounds with alkylating and acylating agents.

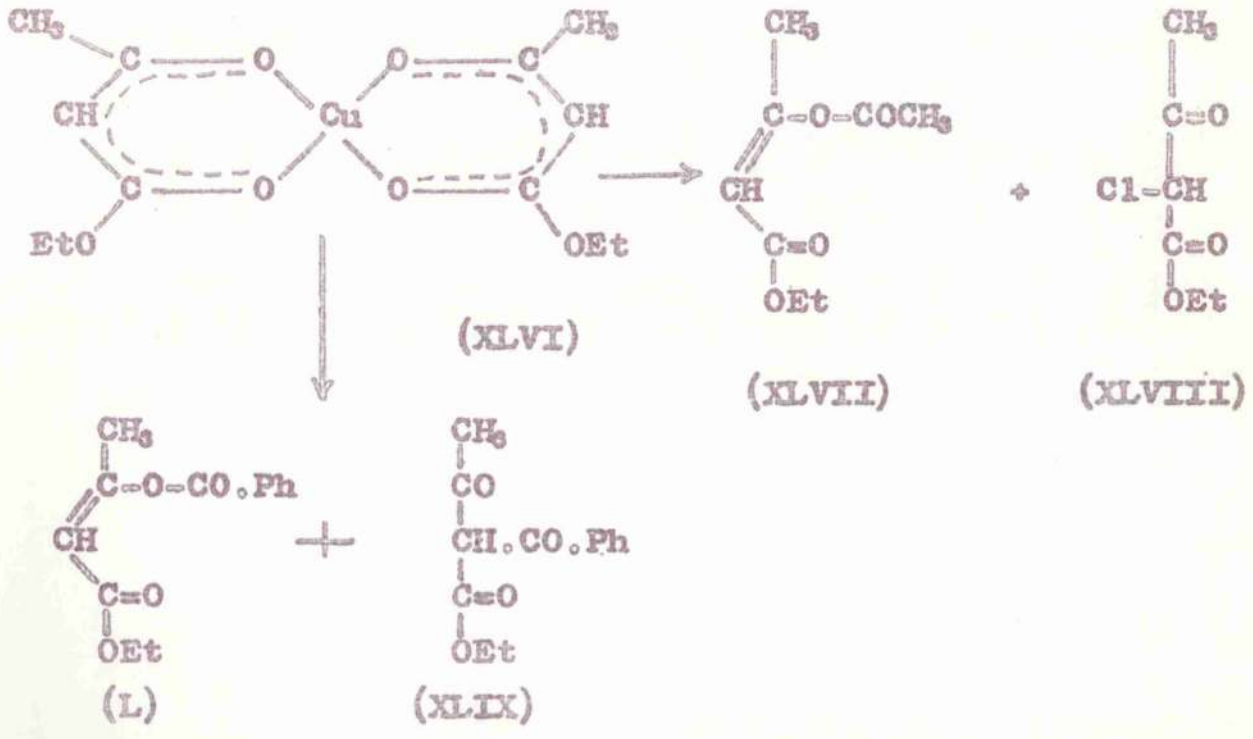
To account for the increased proportion of O- substitution in non-polar solvents, Brändström postulates that if the attacking halide is 'active', that is S_N1 in type, then the polarisation in the transition state, after initial co-ordination, will be sufficient to cause formation of an acyl or alkyl carbonium ion, which will then attack the mesomeric anion at the point of highest electronegativity giving O-substitution mainly. However, the formation of O-substituted products is attributed only to reactions carried out in non-polar solvents, for example ether and benzene. No explanation is given for the absence of

O-substitution in polar solvents, where it might be expected that the formation of carbonium ions would be enhanced by the dielectric constant of the solvent.

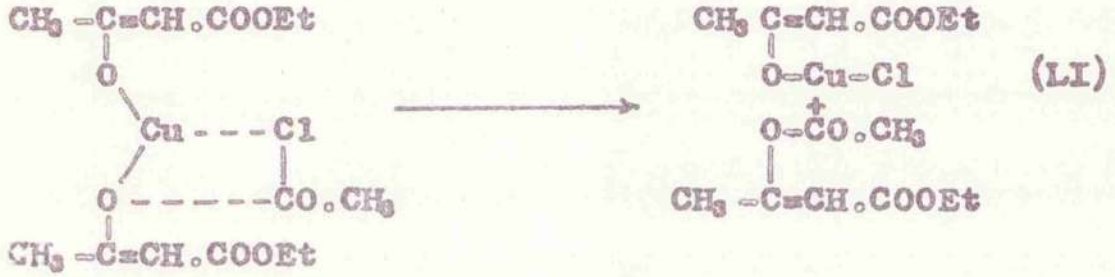
Further, since most of the reactions considered by Brändström were at best semi-quantitative, and carried out solely to prepare the C-substituted product, the possibility of O-substitution in polar solvents cannot be ruled out, especially as Michael[72] reported that the reaction of sodium ethyl acetoacetate with ethyl chloroformate gave O-alkylation in both ether, and ethanol.

In a later paper, Brändström[73] postulated the occurrence of an ionic mechanism, which he defined as being independent of the alkali metal present in the reaction, together with the 'chelate mechanism' described above. This concept was derived from a series of reactions of alkali metal complexes of ethyl acetoacetate with alkyl halides in polar (methanol) and non-polar (t-butanol) solutions. In the latter, it was found that the reaction kinetics varied with variation of the alkali metal in the complex, as would be expected on a basis of the 'chelate mechanism'. However, in methanol the reaction kinetics varied little with variation of the alkali metal, indicating that the kinetics were independent of the metal ion, and that the reaction was ionic in type. In the above discussion no mention is made of the reaction products.

(b) Copper Chelates. Most of the previous work on the reactions of metal complexes of β-dicarbonyl compounds has been concerned with the alkali metal complexes and relatively few examples of the use of copper chelates have been reported. Michael[74] in an investigation of the reactions of the copper chelate of ethyl acetoacetate (XLVI) reported that with acetyl chloride, the chelate gave ethyl O-acetylacetoacetate (XLVII) together with ethyl 3-chloroacetoacetate (XLVIII), whereas with benzoyl chloride a mixture of ethyl C- and O-benzoylacetoacetates (XLIX and L) were isolated. In the latter reaction, Michael reported that the proportion of the ethyl O-benzoyl acetoacetate increased with increasing temperature.

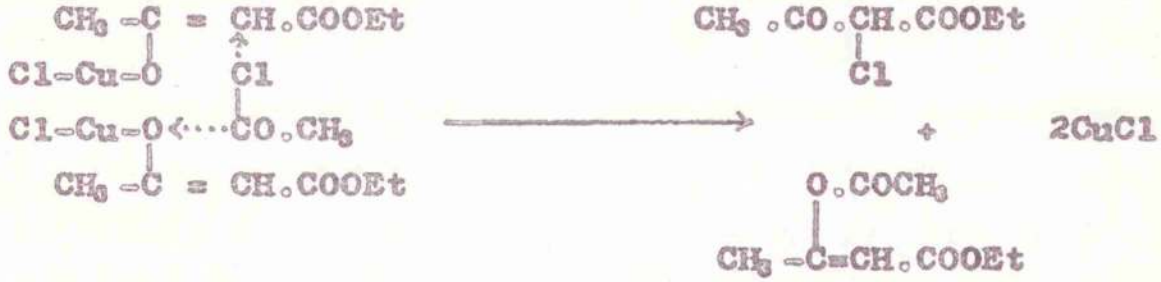


Michael proposed that the reactions involved primary co-ordination of the halogen of the acylating agent to the copper, with resultant attack giving C- or O-acylation depending on the electronic and steric requirements of the acylating groups.



(LI)

Two molecules of the basic copper intermediate (LI) are then envisaged as reacting with a further molecule of the acylating agent to complete the reaction.



Although the mechanism does offer an explanation for the formation of cuprous rather than cupric chloride in the reaction, it relies on the formulation of copper ethyl acetoacetate as a salt rather than a covalent complex. That this is the case is refuted by polarographic reduction evidence showing the covalent nature of the chelate.[39]

A further reaction of a copper chelate of a β-dicarbonyl

compound was described by Nef,[75] who reported the C-substitution of copper ethyl acetoacetate with ethyl chloroformate or chlorodimethylether, these reactions being in direct contrast to the reactions of the sodium chelate, which gives O-alkylation with the above reagents.[76]

In a recent paper, Barry[77] reported that the copper chelates of acetylacetone, benzoylacetone, ethyl acetoacetate, and p-methoxybenzoylacetone, give good yields of the corresponding C-acylated derivatives of the dicarbonyl compounds, when reacted with p-nitrobenzoyl chloride in chloroform. No mention was made of the O-acylated products However, the general claim by Barry that copper chelates of β-dicarbonyl compounds, compared to the corresponding sodium chelates, give better yields of the C-acylated products is contradicted by previous work,[74] and can hardly be substantiated by the use of a limited type of acylating agent.

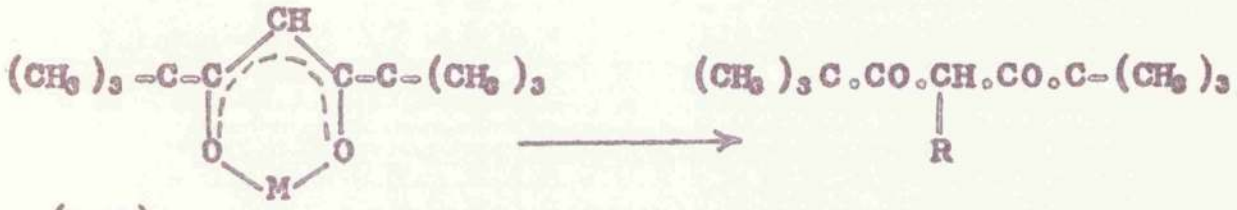
More recently, Nonhebel and Hammond have investigated the reaction of copper dipivaloylmethane with benzoyl and p-substituted benzoyl chlorides. In all cases, the reactions gave the C-acylated product.[26]

(c) Other Metal Chelates. There are various isolated observations scattered through the literature which indicate

that some control of the course of reaction of β-dicarbonyl metal complexes with alkylating and acylating agents is exerted by the metal cations to which the enolate ions are bound. Curtiss[78] reports the reaction of silver acetylacetone with ethyl iodide as giving both C- and O-alkylation, the latter predominating, and this greater tendency of silver complexes, compared with sodium complexes, to give O-substitution has been reported by several workers.[60,71,79,80]

Mention has also been made of some reactions of monovalent thallium complexes of β-dicarbonyl compounds with alkyl[81] and acyl[66] halides, with formation of both C- and O-substituted products, in this case, the former predominating. Magnesium complexes of the β-dicarbonyls have also been used to a limited extent in alkylation and acylation reactions[56,60] with apparent exclusive formation of the C-substituted product.

More recently, Nonhebel and Hammond[26] have shown that the course of reaction can be severely altered by changes in the metal cation of the complex. In a qualitative study of the reactions of various metal chelates of dipivaloylmethane (LII) with a variety of acylating and alkylating agents, the product isolated in every instance, except with the zinc and mercury complexes, was the C-substituted derivative, (LIII).



(LII)

M = $Cu/_2$, $Mg/_2$, $Ni/_2$, Na, Ca, Sn, $Sr/_2$, $Ba/_2$

The zinc and mercury chelates give the O-substituted product (LIV)

(LIV)

Throughout all the above discussions several factors, which influence the course of the reaction of metal chelates of β-dicarbonyl compounds with alkylating and acylating agents, have become apparent. The influence of the metal ion, discussed independently by several workers, has been formulated into a general empirical theory by Nesmeyanov,[69] who stresses the importance of the polarisation of the metal-oxygen bond in the chelate in deciding the direction of the reaction. It is postulated that, if the metal-oxygen bond is strongly ionised, and the reagent is strongly electrophilic (S_N1), O-substitution will occur. Also, if the metal-oxygen bond is not strongly ionised, and the reagent is strongly electrophilic then the O-substitution will be slower, and C-substitution will in some cases

predominate, for example, the C-alkylation of copper ethyl acetoacetate with ethyl chloroformate[75] or chlordimethylether[76]. A similar result is predicted if the metal-oxygen bond is strongly ionised, and the reagent is weakly electrophilic (S_N2) in type. Finally, if the metal-oxygen bond is weakly ionised and the reagent is weakly electrophilic, then O-substitution should again predominate.

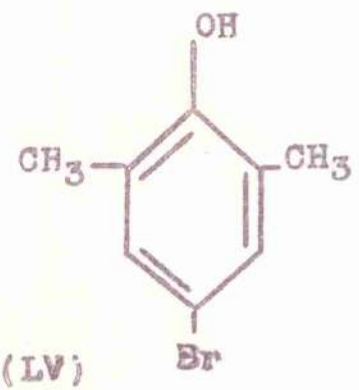
However, many other factors could be expected to influence the above reactions, and it was felt that a brief review of the reactions of metal phenolates with alkylating and acylating agents in which the factors deciding C- and O- substitution have been more fully investigated, might give an indication of the more prominant of these factors, so that the analogous factors in the reactions of metal chelates of β-dicarbonyl compounds could be studied.

Curtin and co-workers,[82] have recently reviewed the factors affecting the ratio of C- to O- alkylation of metal phenoxides. They found that changes in the reaction medium produced changes in the product ratio, a higher proportion of the C-alkyl product being obtained in the order tetrahydrofuran $\ll$ ethanol $<$ ether, benzene.

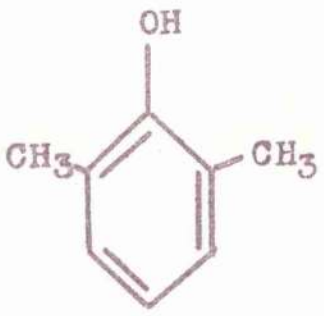
Both Curtin,[82] and Zagorevsky,[83] in quantitative studies,

have shown that the product ratio is influenced by the character of the alkylating agent, the highest proportion of O-alkylated products being given by the most electrophilic (S_N1) halides. The same workers[80,82] have also demonstrated that the metal ion exerts some measure of control over the direction of alkylation, but they report only a limited number of examples.

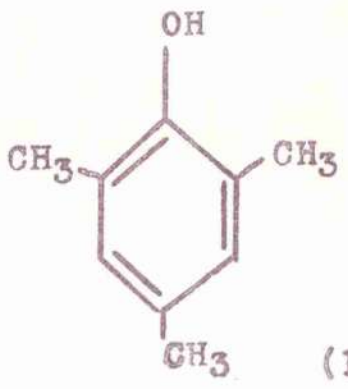
The effect of variations in the structure of the phenol on the product ratio has also been investigated in the series 4-bromo-2,6-dimethyl phenol (LV), 2,6-dimethyl phenol (LVI), and 2,4,6-trimethyl phenol (LVII). In the reactions of the sodium derivatives of these phenols with allyl bromide, the ratio of C- to O-allylation was 0.3, 1.0, 2.7 respectively, indicating an increase in C-alkylation with decreasing phenol acidity.[82] These results are in agreement with the trend observed by Claisen[84] in the alkylation of the sodium salts of phenol and p-methylphenol.



(LV)



(LVI)



(LVII)

Other less obvious factors have been shown to influence the reactions of metal phenoxides with alkylating agents. Curtin[82] indicated that changes in the concentration of the reactants produced changes in the product ratio, and this factor has been expanded and investigated by Kornblum,[85] who demonstrated the importance of the homogeneity or heterogeneity of the reaction on the product ratio. He postulated that true heterogeneous reactions will give only C- alkylation, while homogeneous reactions may give both C- and O-alkylation depending on the other factors discussed above.

THEORETICAL

PART II

GENERAL.

Although the main interest in the present study lies in the reactions of metal chelates of β-diketones with acylating agents, many interesting observations were made in the course of the study relating to the properties of the metal chelates, and since many of these properties may be relevant to any discussion of the reactions of the chelates, an initial survey was felt necessary.

The diketones used in the study were di-isobutyroyl methane (LVIII, R=R'=$CH(CH_3)_2$), benzoylisobutyroylmethane (LVIII, R= Ph, R'=$CH(CH_3)_2$), dibenzoylmethane (LVIII, R=R'=Ph), benzoyl-n-butyroylmethane (LVIII, R = Ph, R' = n-C_3H_7), and di-n-butyroylmethane (LVIII, R=R'=n-C_3H_7).

$$R.CO.CH_2.CO.R'$$

(LVIII)

The copper, nickel, sodium, barium, zinc, and mercury chelates of these diketones were prepared by standard methods with some modifications. With the exception of the mercury complexes the chelates were readily soluble in organic solvents. The introduction of the phenyl substituent into the diketone decreased this solubility, and the chelates of dibenzoyl methane although soluble in toluene, were relatively insoluble in cyclohexane. The majority of the chelates also

have distinct melting points.

The insolubility of the mercury complexes is in agreement with the acyclic structure, as discussed earlier.

The chelates, excluding those of mercury, have similar infrared absorption spectra, showing no 'normal' carbonyl frequency, but showing 'chelate carbonyl absorption'[11,12] in the region 1575-1600 cm.$^{-1}$ indicative of chelation and pseudo aromaticity. In contrast, the mercury complexes exhibit normal carbonyl frequency in the infrared, in the region 1650-90 cm.$^{-1}$ giving further confirmation of the acyclic structure of these complexes. It is perhaps also worthy of note that the diketones themselves show 'chelate carbonyl frequency' in the infrared, showing that these compounds are predominantly in an enolic form with considerable hydrogen bonding between the enolic hydrogen and the second carbonyl group, forming what is in effect a hydrogen chelate.

The ultraviolet absorption spectra of the chelates (Table V) can be used to give an indication of the bonding present in these chelates.

TABLE V

Chelate	λ_{max}^{EtOH}		Chelate	λ_{max}^{EtOH}	
D.I.B.M.	220	272	$Cu(DIBM)_2$	248	296
NaDIBM	218	275	$Ni(DIBM)_2$		298
$Ba(DIBM)_2$		278			
$Zn(DIBM)_2$		272			
$Hg(DIBM)_2$		274			
B.I.B.M.	243	306	$Cu(BIBM)_2$	256	322
NaBIBM	248	308	$Ni(BIBM)_2$	242	328
$Ba(BIBM)_2$	248	308			
$Zn(BIBM)_2$	246	316			
$Hg(BIBM)_2$	248	310			
D.B.M.	251	344	$Cu(DBM)_2$	261	350
NaDBM	251	340	$Ni(DBM)_2$	250	350
$Ba(DBM)_2$	250	343			
$Zn(DBM)_2$	253	340			
$Hg(DBM)_2$	252	343			
B.n.B.M.	244	307	$Cu(BnBM)_2$	256	324
NaBnBM	246	308	$Ni(BnBM)_2$	240	326
$Ba(BnBM)_2$	244	315			
$Zn(BnBM)_2$	244	316			
$Hg(BnBM)_2$	246	314			

D.n.B.M	——	272	$Cu(DnBM)_2$	248	298
NaDnBM	——	272	$Ni(DnBM)_2$	260	298
$Ba(DnBM)_2$	——	277			
$Zn(DnBM)_2$	——	273			
$Hg(DnBM)_2$	——	272			

It can be seen that the sodium, barium, zinc and mercury complexes of the diketones have ultraviolet absorption spectra very similar to those of the corresponding diketone thus indicating that these chelates are predominantly ionic. The nickel chelates although showing similar absorption to the diketones at intermediate wave-lengths, exhibit a bathochromic shift for the maxima corresponding to the higher absorption maxima of the diketones. This is similar to the effect reported by McKenzie and co-workers[13] and illustrates the higher degree of covalency in these chelates. Both maxima for the copper chelates exhibit bathochromic shifts from the corresponding maxima for the diketones indicating a higher degree of covalency of the bonding in these chelates relative to those of nickel. This is in agreement with the recognised order of stability constants for copper and nickel chelates.[5,6]

It is noted that the bathochromic shifts observed in the spectra of the copper and nickel chelates is least for the chelates of dibenzoylmethane, suggesting that the chelates

of this diketone are more ionic than those of the corresponding chelates of the other diketones.

It was observed in the course of the study, that solutions of the nickel chelates of di-isobutyroylmethane, and di-n-butyroylmethane in non-polar solvents undergo a change in colour from green to red as the temperature is raised to 50-60°. This change for the former compound has already been reported by Cotton[35] who attributes it to molecular association and dissociation in solution. Molecular weight determinations carried out on the nickel chelates in solution at room temperature show them to be trimeric. However, at the temperature of the reactions carried out subsequently (78-80°) it can be assumed that the chelates are monomeric.

Reactions of the Chelates.

From the introduction it is obvious that the problem of C- and O-acylation of metal chelates of β-diketones still requires considerable clarification. Many factors might be expected to influence the product ratio and from the consideration of the reactions of metal phenoxides with acylating agents it was felt that the following factors should be studied as being the most likely to produce significant changes in the product ratio:-

(a) Variation of the metal ion in the chelate.

(b) Steric variations of the organic ligand.

(c) Variations in the nucleophilicity of the C- and O-positions in the chelate.

(d) Variations in the electronic character of the acylating agent.

(e) Variations in the reaction conditions with regard to media and temperature.

In order to determine the relative importance of the above effects a scheme for their isolation and investigation, had to be devised. The effects of variation in media, temperature, and metal ion can be readily separated and investigated. To study the effect of steric variation in the diketone on the product ratio, diketones with straight and branched chain substituents were used. In this way, it was hoped that electronic differences in the chelates from these diketones would be minimised, and that changes in the product ratio could be attributed solely to steric factors.

Further, the use of diketones with aryl and alkyl substituents was designed to give variations in the nucleophilicity of the central carbon atom and the carbonyl oxygen atom.

The effect of variation in the electronic character

of the acylating agent was investigated using p-substituted benzoyl chlorides in the reactions. In this way the steric requirements of the acylating agents are constant and the electronic character can be varied dependent on the p-substituent.

It was also intended that a semi-quantitative study of the reaction rates be made using solutions of picric acid as an external indicator. Any unreacted chelate gives the characteristic yellow colour of the 2,4,6-trinitrophenoxide ion with this solution.

Further, since much of the previous work has been qualitative or at best semi-quantitative, an acceptable quantitative analytical method was necessary for the determination of the product ratio in the reaction mixtures. This was found in the ultraviolet absorption method of Vierordt[86] which, providing pure components are available, gives accurate analyses of the proportion of these components in mixtures containing up to three different compounds. This method was applied to the diketone series using weighed synthetic mixtures of benzoylisobutyroylmethane and its C- and O-benzoyl derivatives, di-isobutyroylmethane and its C- and O-benzoyl derivatives, and also of dibenzoylmethane

and its C- and O-*p*-anisoyl derivatives. The method was found to be accurate to with 5%.

The reactions were carried out by adding a very small excess of the acylating agent to a hot solution of the chelate in the appropriate solvent, and treating subsequently with pyridine and water. The final solution after removal of the pyridine was submitted for ultraviolet analysis as above. In many cases the result obtained was substantiated by a qualitative isolation of the products from the reaction mixture. Each reaction was duplicated.

To carry out the study using the above method, pure samples of the diketones and their C- and O-acylated derivatives had first to be synthesised. The diketones were prepared by a modification of the standard Claisen condensation method, using however, lithamide as the condensing agent and utilising the phenyl rather than the ethyl ester.

$$R.CO.CH_3 + PhOOC.R' \xrightarrow{LiNH_2} R.CO.CH_3.CO.R' + PhOH$$

Improved yields were obtained. The diektones were purified by formation, recrystallisation and hydrolysis of their copper chelates.

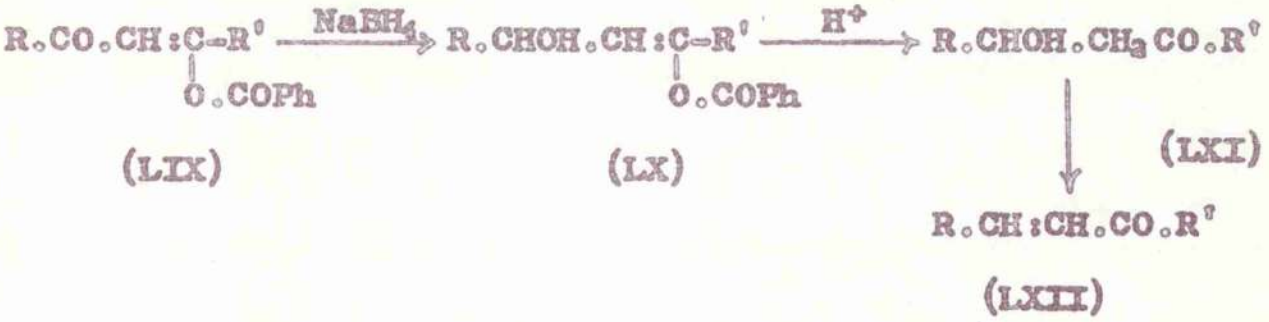
The C-acylated derivatives were prepared by isolation from preliminary qualitative reactions of the copper, nickel or sodium chelates with the appropriate acylating agents.

C-benzoyldi-isobutyroylmethane, being a liquid, was purified through its copper derivative, the remainder by recrystallisation. The C-acylated products in every case give deep red colours with ferric chloride solution, and react with cupric acetate solution to give copper derivatives.

The C-acylated derivatives of the diketones were synthesised by a variation of the method used by Claisen[87] by reacting the β-diketone with the acylating agent in pyridine, with longer reaction times and isolating the product by ether extraction after addition of water and allowing the mixture to stand for several hours to enable complete hydrolysis of any excess of acyl halide and any anhydride formed. The C-benzoates of di-isobutyroyl-methane and di-n-butyroylmethane, being liquids, were purified by chromatography on alumina, the remainder being purified by recrystallisation. None of these compounds gave a colour with ferric chloride solution.

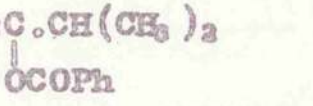
The C- and O-acylated products were easily distinguished by comparisons of the infrared spectra. The former compounds show one carbonyl peak and 'chelate carbonyl' frequency, the latter show αβ-unsaturated carbonyl frequency and also ester carbonyl frequency in the infrared.

To establish the validity of the effect of variation in the electronic character of the chelate on the product ratio, the configuration of the O-acylated derivative (LIX) of the asymmetric diketones used must be known. The configuration of these derivatives can be determined by reducing the carbonyl group to a secondary alcohol (LX) with sodium borohydride in methanol. Subsequent acid hydrolysis of this intermediate will result in the formation of a β-keto-alcohol (LXI) which will readily dehydrate under the reaction conditions to give an αβ-unsaturated ketone (LXII), the structure of which will be dependent on the configuration of the initial O-acylated product.



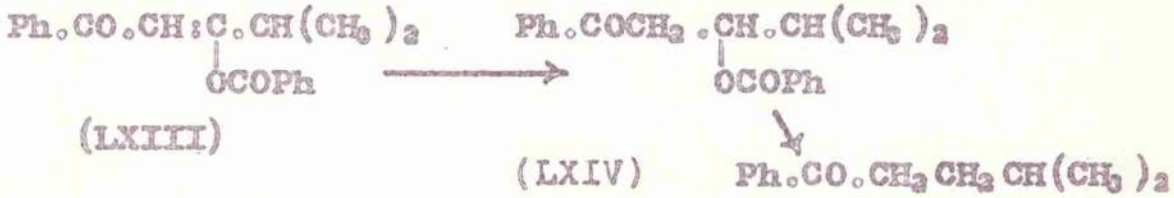
Treatment of O-benzoylbenzoylisobutyroylmethane (LIX, R or R' = Ph or $-CH(CH_3)_2$), as above, gave isopropyl styryl ketone (LXII, R = Ph, R' = $CH(CH_3)_2$) identified by infrared and ultraviolet spectra and vapour phase chromatography comparisons with an authentic specimen, synthesised by condensation of benzaldehyde with methyl isopropyl ketone.[88]

This shows that O-benzoylbenzoylisobutyroylmethane is formed by attack at the carbonyl oxygen in the chelate ring adjacent to the isopropyl substituent, and that its structure is represented by the nomenclature, 3-benzoyloxy-4-methyl-1-phenyl-pent-2-ene-1-one (LXIII).



(LXIII)

That this is the structure of the above compound was confirmed by hydrogenolysis using platinum catalyst in methanol. By this means the O-ester is converted into a saturated ketone by hydrogenation of the double bond and subsequent hydrogenolysis of the enolate ester group. 3-benzoyloxy-4-methyl-1-phenyl-pent-2-ene-1-one (LXIII) on treatment as above gave phenyl isoamyl ketone (LXIV), identified by conversion to its semicarbazone. This is the expected product based on the structure above.



(LXIII) (LXIV)

It can be seen from Table VI that O-benzoylbenzoyl-n-butyroylmethane has virtually identical infrared and ultraviolet absorption spectra with those of 3-benzoyloxy-4-methyl-1-phenyl-pent-2-ene-1-one, and differing from those

of O-benzoyldibenzoylmethane. It is thus reasonable to

TABLE VI.

O-Benzoylated Product of:-	$\nu_{max.}$ cm.$^{-1}$	$\lambda_{max}^{C_6H_{12}}$ mμ
B.I.B.M.	1750 1700	228, 278
D.B.M.	1745, 1680	244, 300
B.n.B.M.	1750, 1700	228, 278

assume that O-benzoylation in the former compound occurs by attack at the carbonyl oxygen atom adjacent to the alkyl substituent in the chelate ring, as in the case of the O-benzoylation in the benzoylisobutyroylmethane series, and not at the phenyl carbonyl group in the chelate as occurs in the dibenzoylmethane series. This means that the O-benzoyl derivative of benzoyl-isobutyroylmethane has a structure represented by the nomenclature 3-benzoyloxy-1-phenyl-hex-2-ene-1-one (LXV).

(LXV)

This configuration is substantiated by an absolute identification of the O-acetyl derivative of benzoyl-n-butyroylmethane by hydrogenolysis as above.[89] In this case also, acetylation occurs at the carbonyl oxygen atom adjacent to the n-propyl substituent of the diketone.

In many of the reactions carried out, varying percentages of the starting diketone were present in the final reaction mixture. The presence of this diketone must be explained to justify the actual product ratio used in determining the mechanism for the reaction. The diketone can be derived by hydrolysis, of the chelate during the reaction, of any unreacted chelate after reaction, or of the C- or O-acylated products either during the reaction or in the course of isolation.

However, if the diketone was formed by hydrolysis of the chelate either during or after the reaction, the percentages of both C- and O-acylated products in the reaction mixture would decrease as the diketone content increased. In fact it is found that the percentage of the C-acylated product remains constant within the experimental error, irrespective of the diketone content, the percentage of the O-acylated product decreasing or increasing to maintain this constancy.

Similarly, if the diketone was formed by hydrolysis of the C-acylated product, it would be expected that the percentage of this product would be dependent on the diketone content. This is not the case. Further, it is also significant that in reactions which give a high

percentage of the C-acylated product, little or no diketone is formed.

Hence the presence of the diketone can only be rationalised by considering it to be formed by hydrolysis of the O-acylated product. This hydrolysis will not affect the percentage of C-acylated product in the reaction mixtures, giving a decrease in the percentage of the O-acylated product with increasing diketone content. This is in excellent agreement with the experimental facts, (see experimental pp182-5). It is not confirmed whether this hydrolysis occurs during reaction or in the course of isolation. However, if the O-benzoates are allowed to stand for 24 hr. in pyridine-water, partial hydrolysis to the diketone occurs. The C-benzoyl derivatives were recovered unchanged after similar treatment.

Finally, the highest percentage hydrolysis occurs in reactions of the zinc and copper chelates. This can be attributed, in the former case, to the action of the very hygroscopic zinc chloride formed in the reactions. A cold solution of anhydrous zinc chloride and 3-benzoyloxy-1-phenyl-hex-2-ene-1-one was allowed to stand for 24 hr. Subsequent ultraviolet analysis of the reaction mixture showed that 80% of the O-benzoylated derivative had been hydrolysed to the diketone. In a similar reaction using

the C-benzoylbenzoyl-n-butyroylmethane, the starting material was recovered unchanged.

In the reactions of the copper chelates as will be described later, hydrogen chloride is evolved, and in presence of traces of moisture will readily hydrolyse the relatively easily hydrolysed O-esters. It can be concluded from the above that the presence of diketone in the reaction mixtures can be attributed to a secondary hydrolysis of the O-acylated product once formed, and that a true representation of the product ratio is given by the percentage C-acylated product.

The development of the theories for the mechanism of the reactions of metal chelates of β-diketones with alkylating and acylating agents has been discussed in the introduction. From the present study an extension of these theories has been evolved based on, and incorporating, the effects of the various factors listed above on the product ratio.

METAL ION EFFECT

The effect of variation in the metal ion in the chelate on the product ratio was studied over a small but representative range of metals, using the transition metals copper, (divalent, pentaco-ordinate), nickel (divalent, hexaco-ordinate), the alkali metal sodium (monovalent, tetraco-ordinate), the alkali earth metal barium (divalent, hexaco-ordinate), the transition metal mercury (divalent tetraco-ordinate) and the fringe transition metal zinc (divalent tetraco-ordinate). From the results in Table VII it is immediately obvious that the metal ion in the complex, as expected, exhibits an important degree of control of the product ratio in the reactions with acylating agents.

TABLE VII

Figures in this and all subsequent tables are percentage C-acylated product averaged from two reactions

Metal	D.I.B.M.	B.I.B.M.	D.B.M.	B.n.B.M.	D.n.B.M.
Cu	99.0	47.5	31.5	30.5	34.5
Ni	83.5	43.0	31.0	44.5	35.5
Na	79.5	68.0	47.0	39.5	42.0
Ba	86.0	42.0	36.0	32.5	35.5
Zn	18.0	28.5	22.0	12.5	0.0
Hg	11.0	22.5	18.0	8.0	0.0

D.I.B.M. di-isobutyroylmethane, B.I.B.M. benzoylisobutyroyl methane, D.B.M. dibenzoylmethane, B.n.B.M. benzoyl-n-butyroyl methane, D.n.B.M. Di-n-butyroylmethane.

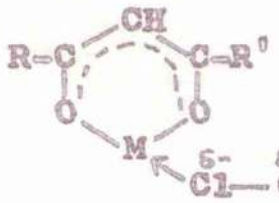
All reactions carried out in cyclohexane.

The copper, nickel, sodium and barium chelates in all cases give a higher percentage of the C-benzoylated derivative, than the corresponding chelates of zinc and mercury, with the sodium chelate usually giving the highest percentage.

It is envisaged, that in the reactions of acylating agents with metal chelates of β-diketones, initial attack occurs at the metal ion in every case. This is substantiated by the inability of the triketonates of ferric iron, and aluminium to react with acylating agents even after

prolonged reaction at high temperatures.[86] This unreactivity can only be attributed to the effective shielding of the metal from attack by the closely packed organic ligands.

In the case of metals which have a maximum co-ordination greater than that required for chelation, for example, copper, nickel, sodium, barium, this attack at the metal is envisaged as resulting in co-ordination of the acyl halide to the metal giving a reaction intermediate (LXVI).



M = Cu/2, Ni/2, Ba/2, Na

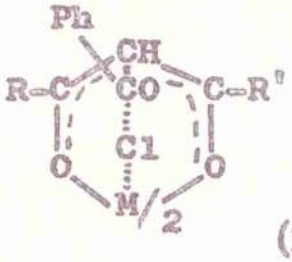
(LXVI)

That reaction proceeds through co-ordination intermediates is substantiated by the relative reaction times for the above reactions. In all cases the order of reactivity is Barium $\rangle$ sodium, nickel $\gg$ copper.
This order is the one which might be expected for co-ordination ability, the barium ion being the largest and therefore the most accessible, and the copper with its weak fifth co-ordination being least likely to react.

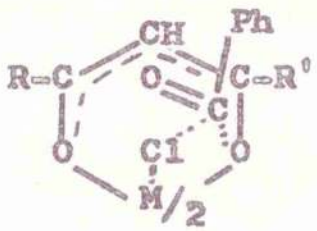
That reaction occurs through co-ordinate transition states for the above metals is further substantiated by the inability of benzoyl chloride to react with either copper or

nickel di-isobutyroylmethane in presence of pyridine, even if a large excess of the acylating agent is used. This can be attributed to the formation of strong solvates of these metal chelates with pyridine, which have been mentioned previously,[23] preventing co-ordination of the benzoyl chloride.

This co-ordination, of the acylating agent to the metal, will result in an increase in the polarisation of the chlorine-carbon bond in the acylating agent giving the carbonyl carbon atom a residual partial positive charge, as proposed by Brändström for the reactions of the sodium chelates.[26] This charged carbon atom, in turn, will be attracted by the π-electrons in the chelate ring, giving cyclic transition states (LXVII), and (LXVIII) by interaction with the central carbon and carbonyl oxygen atoms respectively. This differs from the mechanism proposed by Brändström, who did not admit the formation of the transition state (LXVIII).



(LXVII)



(LXVIII)

The amount of each transition state formed will vary depending on the factors previously enumerated, as will be described later.

In the cases of zinc and mercury, whose maximum co-ordination number is exactly that required for chelation, initial attack at the metal ion must result in a breaking of the metal-oxygen bond in the chelate with formation of a new metal-halogen bond, and an acyl carbonium ion, which will react preferentially at the atom of highest electronegativity in the anion, that is the oxygen atom, to give predominantly O-acylation, as is observed. The high Lewis acid activity of these metals will enhance the polarisation of the chlorine-carbon bond in the acylating agent facilitating the formation of an acyl carbonium ion, and in this respect they are very much like the silver chelates, which are reported as reacting to give mainly O-substitution.[60,72,79,80]

The reaction times for the reactions of the zinc and mercury chelates follow no set pattern as might be expected on the basis of lack of co-ordination with these compounds.

It is evident from the above that the product ratio can be altered to give preferentially C- or O-acylated derivatives by suitable choice of metal in the chelate, with the metals which can react by the co-ordination mechanism giving much more favourable ratios of C- to O- acylated product than those which cannot increase their co-ordination.

In the reactions of the copper chelates, hydrogen chloride is evolved, and the inorganic product of reaction is cuprous rather than cupric chloride. The formation of cuprous chloride has already been observed by Michael[74] but it is evident that, contrary to the theories proposed by Michael, the formation of cuprous chloride is a secondary effect caused by reaction of the cupric chloride, formed initially, with the solvent. A precedent for this has been established by Kochi[90] who showed that cupric chloride reacted with acetone to give chloroacetone, hydrochloric acid, and cuprous chloride.

$$2CuCl_2 + CH_3.CO.CH_3 \longrightarrow CH_3.CO.CH_2Cl + HCl + Cu_2Cl_2$$

Recent studies[91] have shown that anhydrous cupric chloride reacts with several solvents with formation of cuprous chloride and hydrogen chloride, and it would appear that any solvent, such as cyclohexane, with sufficiently available hydrogen atoms can undergo reaction with formation of these products. That the formation of cuprous chloride is a secondary reaction is substantiated by the fact that reaction of copper di-isobutyrcylmethane and p-nitrobenzoyl chloride in cyclohexane carried out at room temperature gave mainly cupric chloride as the inorganic product.

It is interesting to note from the above that the

formation of ethyl 3-chloroacetoacetate in the reaction of copper ethyl acetoacetate with acetyl chloride as described by Michael above, can be derived from the reaction of cupric chloride with any ethyl acetoacetate formed by hydrolysis of any O-acetyl product formed.

STERIC FACTORS IN THE LIGAND

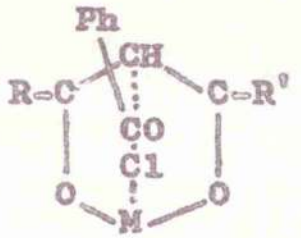
The effect of steric changes in the chelate on the product ratio was studied by comparisons of the reactions of the di-isobutyroylmethane chelates with the corresponding reactions in the di-n-butyroylmethane series, and by comparisons of the reactions of the chelates of benzoylisobutyroylmethane with the corresponding reactions in the benzoyl-n-butyroylmethane series. It was assumed that electronic differences in the two series being compared in each case would not be significant, and therefore that any change in the product ratio can be attributed to steric factors.

It can be seen from the results in Table VIII that the copper, nickel, sodium and barium chelates of di-isobutyroylmethane give a much greater percentage of C-benzoylated product with benzoyl chloride than the corresponding chelates in the di-n-butyroylmethane series.

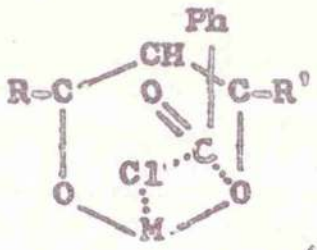
TABLE VIII		
Metal	D.I.B.M.	D.n.B.M.
Copper	99.0	34.5
Nickel	83.5	35.5
Sodium	79.5	42.0
Barium	86.0	35.5
Zinc	18.0	0.0
Mercury	11.0	0.0
Abbreviations as before. Reactions carried out in cyclohexane.		

From a consideration of the mechanism proposed above, the above differences in the product ratios can be rationalised. The transition state (LXVII), formed in the reactions of chelates in which the metal ion has a co-ordination number greater than that required for chelation, involves interaction of the co-ordinated acylating agent with the central carbon atom of the chelate ring. From an examination of models of the system it can be seen that there is only slight steric interaction between the phenyl group and even bulky substituents (R and R') on the diketone. The transition state (LXVIII) on the other hand involves interaction with the oxygen atom of the chelate ring, and a study of models of the system shows that the phenyl group of the acylating agent interferes much more

with the diketone substituent (R'). However, the highest electron density in the chelate ring must be at the more electronegative oxygen atoms, especially in non-polar solvents, in which the charge separation is minimised, and hence a balance between steric interaction prohibiting the formation of the transition state (LXVIII) and the more favourable charge distribution at the oxygen atom will decide the amount of each transition state formed.



(LXVII)



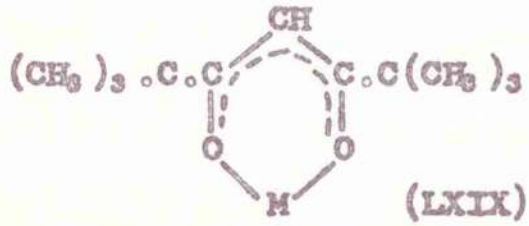
(LXVIII)

M = Cu/2, Ni/2, Na Ba/2

Hence the difference in the product ratios from the reactions of the copper, nickel, sodium and barium chelates of di-isobutyroylmethane and di-n-butyroylmethane can be attributed to a reduction of the steric factor inhibiting the formation of the 4-centred intermediate (LXVIII) by reduction of the steric requirements of the diketone substituent. Since this reduction in the steric factor will make no difference to the formation of the intermediate (LXVII), the net result will be an increase in the amount of the intermediate (LXVIII) formed after co-ordination, with

resultant increase in O- benzoylation, as is observed.

Further evidence for the effect of steric changes in the diketone on the product ratio can be abstracted from the literature. The copper, nickel, sodium, and barium chelates of dipivaloylmethane (LXIX) in which the steric inhibition of the 4-centred intermediate (LXVIII) can be taken to be a maximum, give virtually theoretical yields of the C-benzoylated product on reaction with benzoyl chloride in cyclohexane.[26] Although the electronic nature of the chelates in this series cannot be assumed to be the same as for the above series, the change will not be sufficiently large to invalidate the conclusions regarding the steric effect.



M=Cu/2, Ni/2, Na, Ba/2

(LXIX)

A similar reduction in C-benzoylation is observed for the reactions of the copper, nickel sodium and barium chelates of benzoyl-n-butyroylmethane, compared with benzoylisobutyroylmethane, with benzoyl chloride, as is shown in Table IX.

TABLE IX

Metal	B.I.B.M.	B.n.B.M.
Copper	47.5	30.5
Nickel	43.0	44.5
Sodium	68.0	39.5
Barium	42.0	32.5
Zinc	28.5	12.5
Mercury	22.5	8.0

Abbreviations as before. Reactions carried out in cyclohexane.

In this comparison the effect is not as marked, but is significant for all reactions except nickel. The lesser extent of the change in product ratio may be due to a statistical factor, as in this case, only one alkyl diketone substituent is available for O-benzoylation, compared with two in the above comparison.

It is evident from the above, that steric factors do influence the product ratio of the reactions of β-diketone chelates of metals, whose co-ordination number is greater than that required for chelation, with C-acylation being favoured if the steric requirements of the diketone substituents are large, and O-acylation being favoured if such requirements are small, all other influencing factors being equal.

In the cases of the chelates of metals whose co-ordination number is that required for chelation, and which therefore react through an acyl carbonium ion, rather than through cyclic transition states, less dependence on the steric requirements of the diketone is envisaged, as is observed in the reactions of the zinc and mercury chelates, Tables VIII and IX.

ELECTRONIC FACTORS IN THE LIGAND

The effect of electronic changes in the diketone on the product ratio can be derived from a comparison of the reactions of di-isobutyroylmethane chelates with benzoyl chloride, with those of the corresponding reactions of the benzoylisobutyroyl chelates, and a similar comparison of the reactions of the chelates of benzoylisobutyroylmethane, and benzoyl-n-butyroyl methane with the same reagent. These comparisons are valid in that O-benzoylation occurs at the carbonyl oxygen atom of the chelate ring adjacent to the alkyl group in each case, as shown earlier.

It can be seen from Table X that the copper, nickel, sodium and barium chelates of di-isobutyroylmethane give higher percentages of the C-benzoylated product than the corresponding chelates of benzoylisobutyroylmethane. Since the steric factors for the formation of the co-ordination

TABLE X		
Metal	D.I.B.M.	B.I.B.M.
Copper	99.0	47.5
Nickel	83.5	43.0
Sodium	79.5	68.0
Barium	86.0	42.0
Zinc	18.0	28.5
Mercury	11.0	22.5
Abbreviations as before. Reactions carried out in cyclohexane.		

intermediates are the same for both series, the above difference can be attributed to the replacement of the isopropyl substituent in the diketone, by phenyl. This phenyl group can be expected to exert the same influence in the chelate as in benzoic acid, that is an acid strengthening inductive effect, compared with isobutyric acid, since any mesomeric effects will destabilise the chelates as described in the introduction. That the phenyl group does exert an electron-withdrawing influence is substantiated by the ultraviolet spectra of the copper chelates of the diketones, (p.118.). The bathochromic shift of the maxima in these chelates from the corresponding

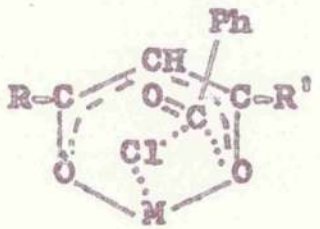
maxima for the diketone, the extent of which is indicative of stability, is least for the copper chelate of dibenzoylmethane and greatest for the copper chelates of di-isobutyroylmethane and di-n-butyroylmethane, with the copper chelates of benzoylisobutyroylmethane and benzoyl-n-butyroyl methane shewing intermediate values.

A further substantiation is given by the fact that in the benzoylation of the chelates of the asymmetric diketones, attack occurs at the carbonyl oxygen atom of the chelate ring adjacent to the alkyl substituent, indicating that this oxygen is the most electronegative atom in the chelate ring.

Hence the introduction of the phenyl substituent will cause an electron-withdrawing inductive effect in the chelates of benzoylisobutyroylmethane, with a resultant decrease in the neutralisation of the residual positive charge on the metal ion in these chelates, relative to that in the di-isobutyroylmethane series. Therefore, on co-ordination of the benzoyl chloride the polarisation of the chlorine-carbon bond will also be increased relative to the polarisation in the di-isobutyroylmethane series, with a resultant greater positive charge being associated with the carbonyl carbon atom of the acylating agent.

This increased charge will enhance the formation of the intermediate (LXVIII) by attacking the chelate ring at the atom of highest electronegativity, that is the oxygen

atom adjacent to the alkyl substituent.



M = Cu/2, Ni/2, Ba/2, Na

(LXVIII)

Alternatively, the increased polarisation may result in the formation of a higher proportion of acyl carbonium ions, from the acylating agent, with similar results.

The replacement of the second isopropyl substituent by phenyl, giving the dibenzoylmethane series of chelates, results in a further increase in O-benzoylation in the reactions with benzoyl chloride. However, this comparison is less valid in that O-benzoylation in this series occurs at the oxygen in the chelate ring adjacent to a phenyl group, with consequent alteration of the steric factors.

The comparison of the reactions of the chelates of di-n-butyroylmethane and benzoyl-n-butyroylmethane with benzoyl chloride is shown in Table XI.

By similar arguments to those used above, it might be expected that the copper, nickel, sodium and barium chelates of di-n-butyroylmethane would give higher percentages of the C-benzoylated derivatives than the

TABLE XI

Metal	B.n.B.M.	D.nB.M.
Copper	30.5	34.5
Nickel	44.5	35.5
Sodium	39.5	42.0
Barium	32.5	35.5
Zinc	12.5	0.0
Mercury	8.0	0.0

Abbreviations as before. Reactions carried out in cyclohexane.

corresponding chelates in the benzoyl-n-butyroylmethane series. This is the case for all chelates except nickel. However, the effect is masked by the availability of both oxygen atoms facilitating the formation of the O-benzoylated product, in the former series.

It can be seen from the above, that the steric inhibition of the formation of the 4-centred intermediates (LXVIII) can be overcome by increasing the charge difference between the carbon atom of the acylating agent and the π-electrons of the chelate ring, by suitable replacement of the diketone substituents. Higher percentages of O-acylated product are obtained as the electron withdrawing properties of the substituent increase, that is as the neutralisation of the residual positive charge on the metal ion decreases. This

dependence of the product ratio on the neutralisation has previously been postulated by Nesmeyanov and Kabachnik.[89]

Again for the reactions of the zinc and mercury chelates, which do not react through cyclic transition states, no such trend is observed. (Tables X and XI). In fact for these chelates, the trend is the reverse of that for the copper, nickel, sodium and barium chelates.

EFFECT OF CHANGES IN THE ELECTRONIC CHARACTER OF THE ACYLATING AGENT.

The effect of changes of the electronic character of the acylating agent, on the product ratios from the reactions with metal chelates of β-diketones, was studied using p-nitrobenzoyl chloride and p-anisoyl chloride. In this way the electronic character of the acylating agent is changed from S_N2 to S_N1 without any corresponding change in the steric requirements of the acylating agent. It can be seen from Table XII that these changes in the acylating agent have a marked effect on the product ratio.

In all the reactions studied, the chelates, with the exception of zinc dibenzoylmethane, give a much lower percentage of the C-acylated product with p-anisoyl chloride, than with benzoyl chloride and a much higher percentage with

TABLE XII

Chelate	p-NO_3	Benzoyl	p-MeO
$Cu(DBM)_2$	-	31.5	1.0
$Ni(DBM)_2$	-	31.0	1.0
NaDBM	80.0 (isol)	47.0	11.5
$Zn(DBM)_2$	-	22.0	33.5
$Cu(BnBM)_2$	80.5	30.5	5.5
$Ni(BnBM)_2$	81.5	44.5	6.5
NaBnBM	85.0	39.5	14.0
$Zn(BnBM)_2$	80.5	12.5	6.5
$Cu(DIBM)_2$	92.0 (isol)	99.0	-
NaDIBM	92.0 (isol)	79.5	-

Abbreviatins as before. Reactions carried out in cyclohexane.

p-nitrobenzoyl chloride. In the cases of the copper, nickel, and sodium chelates this trend is in excellent agreement with the co-ordination theory proposed. It is expected that p-anisoyl chloride, which undergoes hydrolysis by an S_N1 mechanism, will form a much greater proportion of acyl carbonium ion, after co-ordination, than benzoyl chloride with resultant increase in O-acylation.

Conversely, it is also evident that p-nitrobenzoyl chloride, which undergoes hydrolysis by an S_N2 mechanism,

will resist the formation of an acyl carbonium ion after co-ordination, and will therefore favour reaction through the cyclic transition states with resultant increase in C-acylation.

It is interesting to note the times of reaction in the above study. For the copper, nickel, and sodium chelates the order of reaction was:-

p-nitrobenzoyl $\rangle\rangle\rangle$ benzoyl $\rangle$ p-anisoyl

in agreement with an S_N2 mechanism.

More difficulty was found in rationalising the results of the reactions of the zinc chelates, and it is felt that more work must be done before any definite theory could be proposed. The reaction times for the reactions of zinc benzoyl-n-butyroylmethane were in the following order:-

p-anisoyl $\rangle\rangle\rangle$ benzoyl $\langle$ p-nitrobenzoyl

which is opposite to the trend observed with the copper, nickel and sodium chelates, and is indicative of an S_N1 mechanism.

It was found impracticable to study the reactions of the dibenzoylmethane chelates with p-nitrobenzoyl chloride, by the ultraviolet analytical method, because of the tendency of the C-product, p-nitrotribenzoylmethane to

react further with formation of an O-p-nitrobenzoate. However, this ester is easily hydrolysed to the triketone and a semi-quantitative measure of the product ratio was obtained by hydrolysing the reaction mixture from the reaction of the sodium chelate with p-nitrobenzoyl chloride and subsequently isolating the triketone in 80% yield.

Similarly, the C-product was isolated in a state of analytical purity from the reactions of the copper and sodium chelates of di-isobutyroylmethane with p-nitrobenzoyl chloride in over 90% yield.

SOLVENT EFFECTS

The effect of changes in the reaction medium, on the product ratio of the reaction of metal chelates of β-diketones with acylating agents, was studied by carrying out a selection of reactions in cyclohexane (ε = 1.95 at b.p.), ethyl acetate (ε = 5.3 at b.p.) methyl ethyl ketone (ε = 14.5 at b.p.) and ethylene glycol dimethyl ether (ε = 3.3 at b.p.). In all the reactions studied, except those involving copper di-isobutyroylmethane, an increase in C-benzoylation was observed on changing from cyclohexane to ethyl acetate, this increase being greatest for the chelates of dibenzoylmethane. However, it is also noted that a

similar increase in C-benzoylation occurs when the reactions are carried out in ethylene glycol dimethyl ether, which has a low dielectric constant, but a high co-ordination or solvation ability. Hence it would appear that there are two effects associated with the reaction medium, one due to the dielectric constant or polarity of the medium, and one to the solvation ability of the medium. The results are shown in Table XIII.

TABLE XIII

Chelate	C_6H_{12}	Eth. Ac.	D.M.C.	MeCOEt
$Cu(DIBM)_2$	99.0	39.0	-	15.0
NaDIBM	79.4	82.0	-	79.0
$Ba(BIBM)_2$	42.0	44.5	-	-
$Cu(DBM)_2$	31.5	39.5	40.0	-
$Ni(DBM)_2$	31.0	53.5	52.0	-
NaDBM	47.0	70.0	63.5	-
$Ba(DBM)_2$	36.0	59.0	-	-
NaBnBM	40.0	42.5	-	-

C_6H_{12}-cyclohexane, Eth.Ac -ethyl acetate, D.M.C. -ethylene glycol dimethyl ether, MeCOEt - methyl ethyl ketone.

Both the above solvent effects can be rationalised on a basis of the proposed mechanism. As the polarity of the solvent

is increased, charge separation in the cyclic reaction intermediates is facilitated. The increase in polarity will also result in an increase in the ionic character of the chelates which are already predominantly ionic, giving the chelate ring a greater residual negative charge. This charge, due to the greater degree of charge separation, has a correspondingly greater probability of being associated with the central carbon atom of the anion thus favouring C-acylation.

Further, in more polar solvents, the chelates of sodium, barium and nickel are solvated to a greater degree, and in the cases of these metals this solvation will result in the formation of higher co-ordination states. Subsequent displacement of the solvent by the acylating agent can therefore result in the formation of a co-ordination intermediate with a configuration most suitable for cyclisation by interaction with the central carbon atom. The importance of this solvation is evidenced by the reactions in ethylene glycol dimethyl ether.

In opposition to the above effects it might be expected that the formation of an acyl carbonium ion would be enhanced in the more polar solvents giving a higher ratio of O- to C-acylation. From the results it would appear that

the aforementioned effects predominate in the cases of the nickel, sodium and barium chelates. However, it might be expected that a balance between the two opposite effects will be reached. This is evidenced by the product ratio obtained from the reaction of sodium di-isobutyroylmethane with benzoyl chloride in methyl ethyl ketone. Although the dielectric constant of this solvent is much higher than that of ethyl acetate, the percentage of C-benzoylation is fractionally less than that obtained from the corresponding reaction in ethyl acetate.

In the copper chelates which are much more covalent, as has been shown by the ultraviolet study described earlier, a much smaller formal charge will be associated with the ring and the latter effect may predominate as represented by the reactions of copper di-isobutyroylmethane. Further the formation of the higher co-ordination complexes of copper does not change the configuration of the atoms in the chelate. Hence, the copper chelates are not influenced by solvation in the same way as the chelates of nickel, sodium and barium. The fact that copper dibenzoylmethane gives a higher percentage of C-benzoylation with benzoyl chloride in ethyl acetate and ethylene glycol dimethyl ether, than in cyclo-hexane can be attributed to the more ionic nature of this

chelate, compared with copper di-isobutyroylmethane as has been indicated by the study of the ultraviolet spectra of these chelates. However, this increase in C-benzoylation is smaller than the corresponding increases for the reactions of the sodium, nickel and barium chelates of dibenzoylmethane with benzoyl chloride in these solvents.

The above results are in line with those recorded in the literature for acylation reactions of the sodium chelates carried out in ethanol. However, the exceptionally high proportion of C-acylation obtained probably gives a false indication of the product ratio of these reactions. In most cases the reactions were carried out using an excess of acylating agent, and sodium.[41-44] Under these conditions any O-acylated product formed would, in most cases, be hydrolysed to the diketone, which can react further with the excess of sodium and acylating agent, effecting a gradual accumulation of the C-acylated product.

Finally, the above hypothesis regarding the effect of solvent on the reactions is substantiated by a comparison of the reaction times as the polarity of the solvent is increased. In the reactions involving the nickel, sodium and barium chelates a very large decrease in reaction time is observed, with many of the reactions occurring instantaneously in the more polar solvents. This is in agreement with the formation

of solvated complexes from these chelates giving transition states with the correct configuration for C-benzoylation, and also with the more facile charge distribution in the chelate ring, accelerating such benzoylation.

Conversely, the reactions of the copper chelates are not faster in the more polar solvents, indicating that no such favourable configuration is attained in these chelates. In conclusion, it is evident that the product ratio can be altered to favour either C- or O-acylation by a suitable change in the polarity of the reaction medium with the nickel, sodium and barium chelates giving higher ratios of C- to O- acylated products as the polarity of the solvent is increased, within limits. In the reactions of the copper chelates the effect of changes in the polarity of the medium is dependent to a much greater extent on the degree of covalency of the chelate.

Temperature Effects.

The effect of changes of temperature, on the product ratio from the reactions of metal chelates of β-diketones with acylating agents, can be derived from the results shown in Table (XIV). It can be seen that the percentage of the O-benzoylated product increases with increasing temperature in all the reactions studied, the greatest

TABLE XIV

Chelate	80° (ε,1.95)	20° (ε,2.05)
$Ni(BnBM)_2$	44.5	45.0
NaBnBM	39.5	64.5
$Ba(BnBM)_2$	32.5	38.0
$Zn(BnBM)_2$	12.5	44.5
NaDBM	47.0	62.0
$Ba(DBM)_2$	36.0	53.0

Abbreviations as before. All reactions carried out in cyclohexane.

increase being observed for the reactions of the dibenzoylmethane chelates. Unfortunately the reactions of the copper chelates proceed extremely slowly at room temperature and hence could not be studied.

It must be noted that an increase in the temperature of cyclohexane results in a decrease in the dielectric constant, and hence the effect observed above is in the same direction as the one expected on the basis of change of polarity of the solvent. The effects are larger however, than those anticipated on this basis, and it is evident that the reaction temperature does exert a direct measure of control on the product ratio. It has been shown by Dewar[92] that the energy of activation for the

formation of C-alkylated derivatives of β-diketones is higher than the corresponding activation energy for the formation of the O-alkylated product. Hence it might be expected that in identical reactions carried out at different temperatures, O-acylation would be favoured at the higher temperature.

Also, the steric factors, which tend to inhibit the formation of O- rather than C-acylated products can be expected to be reduced at the higher temperature due to the greater molecular movement, thereby favouring the formation of the O-acylated product.

C O N C L U S I O N S.

The above study has shown that many factors do influence the ratio of C- to O-acylated products produced in the reactions of metal complexes of β-diketones with acylating agents. It has been shown that the metal ion in the chelate exerts a marked influence on this product ratio with the copper, nickel, sodium and barium chelates reacting through co-ordination intermediates to give a product ratio dependent on the steric and electronic character of the organic ligand. Conversely, the chelates of zinc and mercury tend to react through an acyl carbonium ion to give more O-acylation than the corresponding reactions above.

In the reactions of the former metal chelates, steric factors associated with the ligand influence the product ratio with C-acylation being favoured if the steric requirements of the ligand are large, and O-acylation being favoured if such requirements are small. Less dependence on the steric nature of the ligand is envisaged for the reactions of the latter chelates.

The product ratio is also influenced for the former chelates by electronic changes in the chelate and acylating agent. It has been shown that if the acylating agent

is S_N1 and/or the residual positive charge on the metal ion is weakly neutralised, O-acylation will result, as is evidenced by the reactions of the copper, nickel, sodium and barium chelates of benzoyl-n-butyroyl methane with p-anisoyl chloride. This trend is in agreement with the emperical rule proposed by Nesmeyanov.[99]

Conversely, if the acylating agent is S_N2 and/or the metal ion in the chelate is strongly neutralised C-acylation predominates, as is evidenced by the reactions of the copper nickel, sodium and barium chelates of benzoyl-n-butyroyl-methane with p-nitrobenzoyl chloride. This trend is contrary to the rule proposed by Nesmeyanov, who predicted that such reactions should give O-acylation.

With acylating agents of character intermediate between S_N1 and S_N2, the product ratio is more dependent on the degree of neutralisation of the metal ion, with C-acylation being favoured as this increases, and O-acylation being favoured as it decreases.

In the reactions of the zinc and mercury chelates O-acylation predominates in all cases irrespective of the degree of neutralisation of the metal.

The effect of the medium on the product ratio has also been studied. It has been shown that the sodium, barium and nickel chelates give increasing C-acylation as the polarity of the solvent increases, within limits. In the reactions of the copper chelates, the effect of changes in the polarity of the medium on the product ratio is dependent on the degree of neutralisation of the metal in the chelate.

It has also been shown that the temperature of the reaction exerts a direct measure of control on the product ratio, with C-acylation being favoured by low temperatures and O-acylation by high temperatures.

From a practical synthetic point of view the above study should enable the best possible choice of reagents and reaction conditions, for the synthesis of triketones, to be made.

EXPERIMENTAL

PART II

PREPARATION

OF

REFERENCE AND STARTING MATERIALS

All m.p. are uncorrected. Infrared spectra were determined in Nujol mull and ultraviolet spectra were determined in ethanol unless otherwise stated. Identities were normally confirmed by infrared comparison in Nujol.

Preparation of β-Diketones.

The β-diketones were prepared by a Claisen condensation of the phenyl or ethyl ester of the appropriate acid, (1 mole) with the appropriate methyl ketone (2 moles) in ether, using lithium amide (2.5 moles) as the condensing agent (Table 1)

Diketone	Ester	Ketone	Yield % Actual	Yield % Lit.
Di-isobutyroyl methane	Phenyl Isobutyrate	Methyl isopropyl	74	26[93]
Benzoyl-iso-butyroylmethane	Phenyl Benzoate	Methyl isopropyl	83	41[94]
Dibenzoylmethane	Obtained as Analar Reagent			
Benzoyl-n-butyroylmethane	Phenyl Benzoate	Methyl n-propyl	67	61[95]
Di-n-Butyroyl methane	Ethyl n-Butyrate	Methyl n-propyl	45	76[96]

The ketone was added to a stirred suspension of the lithium amide in ether (1000 c.c.) at a rate sufficient to cause the ether to reflux gently. The ester was then added

over a period of 15-30 minutes, and the mixture was refluxed for 4-5 hr. After this time the mixtures were grey-black in colour and thick grey slurries were formed. The mixture was then added to iced water, and hydrolysed by addition of hydrochloric acid (10%). The organic layer was diluted with ether, and separated off, washed thoroughly with sodium hydrogen carbonate solution (5%), and water, and dried (Na_2SO_4). The ether was distilled off, and the diketone distilled under reduced pressure. In the preparations involving the phenyl ester, the distilled diketone was washed with saturated sodium carbonate solution to remove traces of co-distilled phenol, dried and re-distilled. In all cases the above preparations are the first reported using lithium amide as a condensing agent. The advantage in using this reagent can be seen by comparisons of the yields of products obtained with those reported using other condensing agents.

Preparation of Chelates

Copper. The copper chelates of the diketones were prepared by shaking a solution of the diketone in ethanol with a saturated solution of copper acetate in water. The chelates separated and were filtered off, washed with water dried and crystallised from solvents such as ether, petroleum ether, or toluene.

Nickel. The nickel chelates were prepared analogously, using nickel acetate. In most cases, however, the nickel complex separated as the dihydrate. This was filtered off, washed with water, dried, and refluxed in toluene in a Dean and Stark apparatus for 3 to 4 hr. The anhydrous chelates were obtained by crystallisation from the toluene.

Sodium. The sodium chelates were prepared by treatment of the diketone with a concentrated solution of sodium hydroxide, sodium di-isobutyroylmethane, using 30%, sodium benzoylisobutyroylmethane, and sodium benzoyl-n-butyroylmethane using 40% solutions. In the case of sodium dibenzoylmethane, the diketone was initially dissolved in ethanol before treatment with 40% sodium hydroxide. Sodium di-n-butyroylmethane was prepared by adding the diketone dropwise to a hot solution of sodium hydroxide (40%). In every case the sodium complex separated as a white amorphous precipitate, which was filtered off, washed sparingly with water, and treated with ether.

Barium. The barium complexes were prepared by adding the diketone to a hot stirred solution of barium hydroxide (10%). The complex usually separated as an off-white amorphous solid, and this was filtered off, washed thoroughly with hot water, dried and crystallised from solvents such as ether, and toluene.

Zinc. These compounds were prepared by adding concentrated ammonia to a solution of zinc acetate and the diketone in aqueous ethanol. Careful addition was necessary to prevent the formation and precipitation of zinc hydroxide. The zinc chelates separated, were filtered off, washed with dilute ammonia, water, dried, and crystallised from solvents such as ether, methanol, chloroform.

Mercury. The mercury complexes were prepared by adding the diketone, in ethanol, to a hot solution of mercuric acetate, from mercuric chloride and sodium acetate. The mercury complex separated out and was filtered off, washed thoroughly with water, dried and crystallised or triturated with solvents such as acetone, ethanol, benzene, and ether.

Chelate	Characteristics	m.p.	Method of Purification
			Recrystallised from:-
$Cu(DIBM)_2$	Blue rhomboids	124 (lit.114[93])	Pet.ether
$Cu(BIBM)_2$	Grey-green needles	168 (lit.168[94])	ether
$Cu(DBM)_2$	Green needles	297 (lit.297[97])	toluene
$Cu(BnBM)_2$	Green needles	134 (lit.131[95])	methanol
$Cu(DnBM)_2$	Blue needles	158 (lit.158[96])	methanol
$Ni(DIBM)_2$	Green needles	172	toluene
$Ni(BIBM)_2$	Green plates	168	toluene/pet. ether

Chelate	Characteristics	m.p.	Method of Purification
			Recrystallised from:-
$Ni(DBM)_2$	Brown amorphous solid	282	toluene
$Ni(BnBM)_2$	Green needles	163-164	toluene
$Ni(DnBM)_2$	Green plates	134	toluene
NaDIBM	White needles	200-201	ether
NaBIBM	White powder	230-232	ether
NaDBM	White powder	350	eluted ether
NaBnBm	White amorphous solid	292-293	ether
NaDnBM	White amorphous solid	>350	ether
$Ba(DIBM)_2$	White rhomboids	194	ether/pet. ether
$Ba(BIBM)_2$	White plates	242	ether/pet. ether
$Ba(DBM)_2$	Yellow amorphous solid	350	toluene
$Ba(BnBM)_2$	White amorphous solid	192-194	ether
$Ba(DnBM)_2$	White amorphous solid	161-163	ether
$Zn(DIBM)_2$	White needles	152	Chloroform/ methanol
$Zn(BIBM)_2$	White needles	114	Chloroform/ methanol
$Zn(DBM)_2$	White needles	220	benzene
$Zn(BnBM)_2$	White needles	120	methanol
$Zn(DnBM)_2$	White powder	148	ether
$Hg(DIBM)_2$	White amorphous solid	208-210	acetone

Chelate	Characteristics	m.p.	Method of Purification
			Recrystallised from:-
$Hg(BIBM)_2$	White needles	172-173	ethanol
$Hg(DBM)_2$	White amorphous solid	296-300	Eluted with hot benzene
			Recrystallised from:-
$Hg(BnBM)_2$	White amorphous solid	140-142	ethanol
$Hg(DnBM)_2$	White amorphous solid	220 (decomp)	acetone

DIBM - di-isobutyroylmethane, BIBM - benzoylisobutyroylmethane

DBM - dibenzoylmethane, BnBM - benzoyl-n-butyroylmethane,

DnBM - di-n-butyroylmethane.

Ultraviolet Spectra of the Metal Chelates

Chelate	λ_{max}^{EtOH} mμ		
DIBM	——	220 (ε,7,200)	272 (ε,11,700)
$Cu(DIBM)_2$	204(ε,9,300)	248 (ε,15,500)	296 (ε,21,500)
$Ni(DIBM)_2$	204 (ε,2,100)	———	298 (ε,3,200)
NaDIBM	———	218 (ε,3,500)	275 (ε,4,500)
$Ba(DIBM)_2$	204 (ε,2,300)	———	278 (ε,15,500)
$Zn(DIBM)_2$	204 (ε,1,500)	———	272 (ε,22,400)
$Hg(DIBM)_2$	210 (ε,10,000)	———	274 (ε,12,500)

Chelate	λ_{max}^{EtOH} mμ		
BIBM	206 (ε,13,000)	243 (ε,6,300)	306 (ε,18,500)
$Cu(BIBM)_2$	206 (ε,15,300)	256 (ε,19,900)	322 (ε,25,900)
$Ni(BIBM)_2$	206 (ε,11,500)	242 (ε,20,200)	328 (ε,26,300)
NaBIBM	206 (ε,12,300)	248 (ε,11,200)	308 (ε,31,800)
$Ba(BIBM)_2$	206 (ε,22,400)	248 (ε,12,300)	308 (ε,32,600)
$Zn(BIBM)_2$	205 (ε,14,000)	246 (ε,14,000)	316 (ε,33,700)
$Hg(BIBM)_2$	209 (ε,15,000)	248 (ε,9,900)	310 (ε,8,300)
DBM	205 (ε,17,100)	251 (ε,9,000)	344 (ε,27,000)
$Cu(DBM)_2$	205 (ε,2,200)	261 (ε,1,900)	350 (ε,3,800)
$Ni(DBM)_2$	204 (ε,4,600)	250 (ε,2,700)	350 (ε,4,500)
NaDBM	204 (ε,12,500)	251 (ε,7,100)	340 (ε,21,000)
$Ba(DBM)_2$	204 (ε,25,000)	250 (ε,12,500)	343 (ε,36,000)
$Zn(DBM)_2$	205 (ε,31,000)	253 (ε,16,500)	340 (ε,52,000)
$Hg(DBM)_2$	206 (ε,14,500)	252 (ε,7,000)	343 (ε,4,400)
BnBM	205 (ε,9,500)	244 (ε,6,000)	307 (ε,12,000)
$Cu(BnBM)_2$	210 ———	256 (ε,27,000)	324 (ε,33,500)
$Ni(BnBM)_2$	208 (ε,20,000)	240 (ε,19,300)	326 (ε,24,000)
NaBnBM ($CHCl_3$)	———	246 (ε,2,800)	308 (ε,7,200)
$Ba(BnBM)_2$	208 (ε,16,700)	244 (ε,12,000)	315 (ε,25,600)
$Zn(BnBM)_2$	210 (ε,29,400)	244 (ε,14,700)	316 (ε,31,300)
$Hg(BnBM)_2$	———	246 ———	314 ———

Chelate	λ_{max}^{EtOH} mμ		
DnBM	204 ———	———	272 (ε,6,200)
$Cu(BnBM)_2$	210 (ε,9,700)	248 (ε,15,500)	298 (ε,23,000)
$Ni(BnBM)_2$	210 (ε,7,600)	260 (ε,6,300)	298 (ε,18,500)
NaDnBM	204 ———	———	272 (ε,9,000)
$Ba(DnBM)_2$	204 ———	———	277 (ε,19,000)
$Zn(DnBM)_2$	204 ———	———	273 (ε,11,000)
$Hg(DnBM)_2$	210 ———	———	272 ———

Benzoyl Di-isobutyroylmethane. - Copper di-isobutyroylmethane (2.1 g.) in cry cyclohexane was refluxed for 18 hr., with benzoyl chloride (1.3 c.c.). The reaction mixture was then filtered free of inorganic product, and the solvent was distilled off under reduced pressure, to give benzoyl di-isobutyroylmethane, (2.7 g.) as white prisms, recrystallised from petroleum ether (b.p. 40-60°) m.p. 86° (Found: C,73.36 H,7.91. $C_{18}H_{30}O_3$ requires C,73.82; H,7.74%), λ max. 206 (ε,17,000), 252 (ε,18,500) and 282 mμ (ε,14,000); ν max. 1680 (C:O) and 1590 $cm.^{-1}$ (aromatic).

Treatment of benzoyl di-isobutyroylmethane (0.5 g.) in ethanol (25 c.c.) with saturated cupric acetate solution (5 c.c.) gave purple granules of copper benzoyl di-isobutyroyl

methane (0.5 g.) recrystallised from ether as purple plates, m.p. 208-209° (Found: C,66.2; H,6.3. $C_{32}H_{38}O_8Cu$ requires C,66.0; H,6.54%), λmax. 205 (ε,31,400), 250 (ε,26,600), and 300mμ (ε,18,750); νmax. 1650 (C:O), 1560 and 1590 cm.$^{-1}$ (chelate C:O).

O-Benzoyl Di-isobutyroylmethane. - After allowing di-isobutyroylmethane (5 c.c.) in pyridine (5 c.c.), to stand for 24 hr., with benzoyl chloride (4.3 c.c.), water was added, and the mixture left for a further 24 hr., before extracting with ether. The ethereal phase was separated, and washed successively with dilute hydrochloric acid, dilute sodium hydroxide solution, and water, dried and concentrated by distillation. The gum obtained was chromatographed on alumina and the initial fractions eluted by petroleum ether were re-chromatographed on alumina. The initial fractions from the second chromatogram, giving no colour with ferric chloride solution, were evaporated to dryness by distillation under reduced pressure giving O-benzoyl di-isobutyroylmethane (2.6 g.) as a clear oil, (Found: C,74.34; H,7.97. $C_{18}H_{22}O_3$ requires C,73.82; H,7.74%), $\lambda_{max}^{C_6H_{12}}$ 200 (ε,9,000) and 232 mμ (ε,18,300); νmax 1700 and 1754 (C:O and ester carbonyl) and 1625 cm.$^{-1}$ (aromatic).

Dibenzoylisobutyroylmethane. - Benzoyl chloride (1.08 c.c.) was added to a hot solution of sodium benzoylisobutyroylmethane (2 g.) in cyclohexane (100 c.c.), and the mixture was refluxed for 1 hr. On concentrating the solution, dibenzoylisobutyroylmethane (1.2 g.) was obtained as white needles, recrystallised from ether, m.p. 136°, (Found: C,77.6; H,6.36. $C_{19}H_{18}O_3$ requires C,77.53; H,6.16%), λmax. 206 (ε,17,000), 250 (ε,21,000) and 296 mμ (ε,8,500), νmax. 1718, 1680 (C:O) and 1590 cm.$^{-1}$ (aromatic).

3-Benzoyloxy-4-methyl-1-phenylpent-2-ene-1-one (O-Benzoyl benzoylisobutyroylmethane). - Benzoylisobutyroyl methane (5 c.c.) in pyridine (5 c.c.) was allowed to stand for 24 hr., with benzoyl chloride (4.3 c.c.). Water was then added and the mixture allowed to stand for a further 2 hr., before extraction with ether. The ethereal phase was separated, washed thoroughly with water, dilute hydrochloric acid, dilute sodium hydroxide solution, and water, dried, and the ether evaporated giving a yellow oil which crystallised on standing to give 3-benzoyloxy-4-methyl-1-phenyl-pent-2-ene-1-one (2.4 g.), m.p. 59-60° as white prisms, recrystallised from ether, (Found: C,77.4; H,6.4. $C_{19}H_{18}O_3$ requires C,77.5; H,6.2%), λ max. 208 (ε,9,500), 228 (ε,16,000) and 278 mμ (ε,15,800); νmax. 1750 (ester C:O) and 1700 cm.$^{-1}$ (αβ-unsaturated C:O).

Absolute Identification of O-Benzoyl Benzoylisobutyroylmethane. - Sodium borohydride (0.57 g.) in methanol (3.25 c.c.) was added dropwise to a solution of O-benzoyl benzoylisoburyroylmethane (1.143 g.) in methanol (6.5 c.c.), and the mixture was allowed to stand for 2 hr., before being acidified to Congo Red with dilute hydrochloric acid. After acidification, the mixture was heated on a steam bath for 10 min., cooled, and basified by addition of dilute sodium hydroxide solution. The basic phase was extracted with ether, the ethereal phase separated, washed with water, dried and evaporated giving a clear gum, which could not be crystallised. This gum was identified as isopropyl styryl ketone by infrared, and ultraviolet spectra, and vapour phase chromatographic comparisons with an authentic specimen, prepared by condensation of benzaldehyde with methyl isopropyl ketone.[88]

O-Benzoyl benzoylisobutyroylmethane (0.61 g.) in methanol (100 c.c.) was hydrogenated at room temperature and pressure using a platinum catalyst. Reduction took place over 4 hr., in which time 250 c.c. of hydrogen were absorbed (2 mole equivalent). The methanol solution was filtered free from catalyst, and evaporated to dryness, giving a colourless gum, which was identified as isoamyl

phenyl ketone, by conversion to its semicarbazone, m.p. 150-152° (lit., m.p. 150-151°).[98]

Tribenzoylmethane. - This compound was isolated from the reaction of sodium dibenzoylmethane and benzoyl chloride as white needles, m.p. 245° (lit., 241-244°),[42] and recrystallised from chloroform, m.p. 245°.

O-Benzoyl dibenzoylmethane. - Dibenzoylmethane (5.5 g.) and benzoyl chloride (4.3 c.c.) in pyridine (5 c.c.) were allowed to stand for 18 hr. Water and ether were then added, and a yellow solid was precipitated. This was filtered off, washed with ether and water, dried and crystallised from benzene as yellow needles of O-benzoyl dibenzoylmethane (5.7 g.), m.p. 108-109° (lit., 108-109°).[87]

O-Anisoyldibenzoylmethane. - A mixture of dibenzoylmethane (5 g.) and p-anisoyl chloride (7 g.) in pyridine (40 c.c.) was allowed to stand for 48 hr. Water was then added and the mixture left for a further 48 hr. during which, solid separated. This was filtered off and washed with water, and petroleum ether, dried, and crystallised from chloroform-methanol as yellow needles of O-p-anisoyl dibenzoylmethane (5 g.), m.p. 136°, (Found: C, 77.05; H, 5.26. $C_{23}H_{18}O_4$ requires C, 77.08; H, 5.06%), λ max. 208 (ε, 27,500),

268 (ε,26,500), and 274 mμ (ε,26,000), λ inflex. 300 mμ (ε,22,000), ν max. 1666 (unsaturated C:O), 1740 (ester C:O) and 1590 cm.$^{-1}$ (aromatic).

p-Nitrobenzoyldibenzoylmethane. - Sodium dibenzoylmethane (4 g.) and p-nitrobenzoyl chloride (5 g.) were refluxed for 3 hr. in benzene (200 c.c.). The reaction mixture was then filtered, and the solvent distilled off. Ethyl acetate was added, followed by anhydrous potassium carbonate. The mixture was refluxed for 2 hr., water was added and the basic aqueous phase was acidified. The white precipitate formed was collected and dissolved in ether, the ethereal solution being washed thoroughly with sodium bicarbonate solution and water, dried and concentrated giving a clear gum from which p-nitrobenzoyldibenzoylmethane (0.6 g., 10%), m.p. 183-185° (lit., 181-185°)[58] was isolated as yellow plates.

Concentration of the ethyl acetate layer gave O-p-nitrobenzoyl p-nitrobenzoyldibenzoylmethane, (3.4 g.) m.p. 168° (lit., 167-168°)[58] as white plates. This compound on heating with sodium hydroxide solution (0.3N) in aqueous ethanol gave p-nitrobenzoyldibenzoylmethane (2.1 g.), m.p. and mixed m.p. 183-185°.

p-Anisoyldibenzoylmethane. - A mixture of sodium dibenzoylmethane (3 g.) and p-anisoyl chloride (5 g.) were refluxed for 3 hr. in benzene (150 c.c.), The reaction mixture was then filtered, and the benzene solution was washed with sodium bicarbonate solution, sodium carbonate solution, and water, dried and concentrated, with addition of ethanol. A precipitate was obtained and this was triturated with ethanol, and crystallised from acetone as white plates of p-anisoyldibenzoylmethane (0.4 g.), m.p. 204-207° (lit., 205-207°).[58]

Dibenzoyl-n-butyroylmethane. - This compound was isolated from the reaction of sodium benzoyl-n-butyroyl methane and benzoyl chloride in cyclohexane, and crystallised from ether as white plates, m.p. 110-111° (lit., 110°).[99]

3-Benzoyloxy-1-phenyl-hex-2-ene-1-one. - Benzoyl-n-butyroylmethane (5 c.c.) in pyridine (5 c.c.) was allowed to stand for 24 hr. with benzoyl chloride (5.3 g.). Ether was then added, and the ethereal solution washed with ice-cold 2N hydrochloric acid, 2N sodium hydroxide solution, and water, dried and concentrated giving light yellow needles of 3-benzoyloxy-1-phenyl-hex-2-ene-1-one, (3 g.) m.p. 49-50° recrystallised from ether, (Found: C,77.66; H,6.01. $C_{19}H_{18}O_3$ requires C,77.53; H,6.16%), λ max. 208

(ε.12,000), 228 (ε,18,000) and 278 mμ (ε,17,000), ν max. 1750 (ester C:O), 1700 (αβ-unsaturated C:O) and 1620 cm.$^{-1}$ (aromatic).

p-Nitrobenzoylbenzoyl-n-butyroylmethane. - Nickel benzoyl-n-butyroylmethane (2.7 g.) was refluxed for 5 min. with p-nitrobenzoyl chloride (2.5 g.) in cyclohexane (200 c.c.). The reaction mixture was then filtered, and the solvent was distilled off under reduced pressure giving a yellow gum, which crystallised from ether/petroleum ether (b.p. 40-60°) as yellow needles of p-nitrobenzoylbenzoyl-n-butyroylmethane (2.5 g. 61%), m.p. 90-91°, (Found: C,67.3; H,5.01; N,4.35. $C_{19}H_{17}NO_5$ requires C,67,3; H,5.01; N,4.14%), $\lambda_{max}^{CHCl_3}$ 256 (ε,17,000) and 296 mμ (ε,12,500), ν max. 1666 (C:O) and 1600 cm.$^{-1}$ (chelate C:O).

3-p-Nitrobenzoyloxy-1-phenyl-hex-2-ene-1-one. p-Nitrobenzoyl chloride (6 g.) was added to a cooled solution of benzoyl-n-butyroylmethane (5 g.) in pyridine (40 c.c.) and the mixture was allowed to stand for 48 hr. A solid separated out, and this was filtered off, and crystallised from ether to give yellow needles of 3-p-nitrobenzoyloxy-1-phenyl-hex-2-ene-1-one (4 g.), m.p. 83°, (Found: C,67.4; H,4.9; N,3.87. $C_{22}H_{15}NO_3$ requires C,67,25; H,5.05;

N,4.1%), λ max.206 (ε,14,000) and 266 mμ (ε,18,000), ν max 1752 (ester C:O), 1692 (αβ-unsaturated C:O), 1610 and 1550 cm.$^{-1}$ (aromatic doublet).

p-Anisoylbenzoyl-n-butyroylmethane. - Benzoyl-n-butyroylmethane (2 c.c.) and sodium (0.5 g.) were refluxed for 1 hr. in cyclohexane (100 c.c.) with p-anisoyl chloride (1.8 g.). The solvent was then distilled off under reduced pressure, and pyridine, and water added. After allowing the mixture to stand for 2 hr., ether was added and the ethereal solution washed with dilute hydrochloric acid, dilute sodium hydroxide solution, and water, dried and concentrated giving p-anisoylbenzoyl-n-butyroylmethane (0.5 g.), m.p. 124° as white plates, recrystallised from ether. (Found: C,73.96; H,6.31. $C_{20}H_{20}O_4$ requires C,74.05; H,6.2%). λ $^{C_8H_{12}}_{max}$ 208 (ε,17,000), 220 (ε,15,500), 250 (ε,14,500) and 282 mμ (ε,19,000), ν max. 1710, 1682, 1660 (all C:O) and 1600 cm.$^{-1}$ (aromatic).

3-Anisoyloxy-1-phenyl-hex-2-ene-1-one. - A mixture of benzoyl-n-butyroylmethane (5 g.) and p-anisoyl chloride (5 g.) in pyridine (30 c.c.) was allowed to stand for 48 hr. Water was added, and the mixture was extracted with ether, the ethereal phase being washed with dilute hydrochloric acid, sodium hydroxide solution and water, dried, and concentrated

giving 3-anisoyloxy-1-phenyl-hex-2-ene-1-one (4.5 g.), m.p. 72-73° as yellow needles, recrystallised from ether, (Found: C,74.2; H,6.3. $C_{20}H_{20}O_4$ requires C,74.05; H,6.2%), λ max. 210 (ε,22,000) and 274 mμ (ε,30,000), ν max. 1740 (ester C:O) 1700 (unsaturated C:O) and 1610 cm.$^{-1}$ (aromatic).

Benzoyldi-n-butyroylmethane. - Copper di-n-butyroylmethane (6.3 g.) was refluxed in cyclohexane (150 c.c.) with benzoyl chloride (4.75 c.c.) for 3 hr. The reaction mixture was then filtered, and the solvent distilled off under reduced pressure. Pyridine and water were added to the yellow oil obtained, and after allowing this mixture to stand for 2 hr., ether was added. The ether phase was washed with 2N hydrochloric acid, 2N sodium hydroxide solution, and water, dried and concentrated. A gum was obtained, and this was chromatographed on alumina. The fractions eluted with benzene were treated with an aqueous ethanolic solution of cupric acetate, and a solid was obtained, which was crystallised from methanol as blue needles of copper benzoyldi-n-butyroylmethane (1.2 g.), m.p. 172°, (Found: C,65.9; H,6.5. $C_{32}H_{38}CuO_8$ requires C,66.0; H,6.5%), λ max. 210 (ε,28,000), 250 (ε,31,000) and 300 mμ (ε,24,000), ν max. 1650 cm.$^{-1}$ (C:O).

The copper complex was dissolved in ether, and shaken with dilute hydrochloric acid solution. The ether

phase was washed with water, dried and evaporated to dryness, giving benzoyldi-n-butyroylmethane (0.8 g. 9%) as a colourless oil, (Found: C, 74.43; H, 7.7. $C_{16}H_{20}O_3$ requires C, 73.8; H, 7.7%), $\lambda_{max}^{C_6H_{12}}$ 210 (ε, 31,000), 248 (ε, 47,000) and 280 mμ (ε, 34,000), ν_{max} 1666 (C:O) and 1600 $cm.^{-1}$ (chelate C:O)

O-Benzoyl Di-n-butyroylmethane. - A mixture of di-n-butyroylmethane (5 c.c.), and benzoyl chloride (5.3 g.) in pyridine (5 c.c.) was allowed to stand for 18 hr. Ether was then added and the solution washed successively with 2N hydrochloric acid, 2N sodium hydroxide solution and water, dried and evaporated to dryness. A yellow oil was obtained, and was purified by chromatographing on alumina. Petroleum ether eluted a colourless oil, which did not give a colour with ferric chloride solution. This was the required O-benzoyl di-n-butyroylmethane (2 g.), (Found: C, 73.4; H, 7.87. $C_{16}H_{20}O_3$ requires C, 73.8; H, 7.74%), $\lambda_{max}^{C_6H_{12}}$ 206 (ε, 8,800) and 234 mμ (ε, 21,000), ν_{max} 1700 and 1754 $cm.^{-1}$ (C:O and ester C:O).

REACTIONS OF THE CHELATES

Reactions of the Metal Complexes with Acyl Halides.

Unless otherwise stated the reactions were carried out in the dry refluxing solvent, with the metal complexes in quantities giving a 2% solution or suspension. The acyl chloride (1 molar equivalent for the sodium complexes and 2 molar equivalents for the other complexes) was added to the hot solution, and the mixture refluxed until the supernatant liquid no longer gave the characteristic yellow colour of the trinitrophenoxide ion with a saturated solution of picric acid in the corresponding solvent. The reaction mixture was then filtered free from the inorganic product, the solvent was distilled off under reduced pressure, and pyridine containing a trace of water was added. After allowing the mixture to stand for 16-24 hr. the appropriate solvent for ultraviolet analysis (chloroform or cyclohexane) was added and the organic layer washed with water, dilute hydrochloric acid, saturated sodium bicarbonate solution, and water, and dried (Na_2SO_4). The solution thus obtained was submitted for ultraviolet analysis. The results are tabulated in the theoretical section. All reactions were duplicated.

In the reactions carried out at room temperature, the reactants were dissolved in the appropriate solvent, and

were then agitated until the supernatant liquid did not give the yellow colour with picric acid solution.

Check on the Ultraviolet Analytical Method.

Synthetic binary and trinary mixtures of dibenzoylisobutyroylmethane (C-), 3-benzoyloxy-4-methyl-1-phenyl-pent-2-ene-1-one (O-), and benzoylisobutyroylmethane (DK) were made up using a microbalance. The mixtures were then dissolved in cyclohexane and submitted for ultraviolet analysis. The results are shown below:-

	% C-	% O-	% DK
Actual	18.9	81.1	0.0
Calculated	17.3	82.7	0.0
Actual	14.5	68.4	17.0
Calculated	11.6	73.4	15.0
Actual	57.0	43.0	0.0
Calculated	58.0	42.0	0.0

Similarly, mixtures of dibenzoylmethane (DK), O-p-anisoyl dibenzoylmethane (O-), and p-methoxytribenzoyl methane (C-) were carefully made up, dissolved in chloroform and submitted for ultraviolet analysis.

	% C-	% O-	% DK
Actual	0.0	34.7	65.3
Calculated	6.2	28.8	65.0
Actual	48.8	51.2	0.0
Calculated	54.0	43.5	2.5
Actual	24.8	26.1	49.1
Calculated	29.0	23.0	48.0

Further, mixtures of di-isobutyroylmethane (DK), O-benzoyldi-isobutyroylmethane (O-), and benzoyldi-isobutyroylmethane (C-) were weighed out, dissolved in cyclohexane and submitted for ultraviolet analysis.

	% C-	% O-	% DK
Actual	74.0	26.0	0.0
Calculated	70.0	30.0	0.0
Actual	0.0	65.0	35.0
Calculated	0.0	66.5	33.5
Actual	18.6	53.0	28.4
Calculated	21.8	49.0	29.2

Ultraviolet Analyses of Metal Chelate Reactions.

(a) With benzoyl chloride in cyclohexane

Chelate	Reaction Time	% C-	% O-	% DK
$Cu(DIBM)_2$	18 hr.	99.4, 99.0	0.6, 0.0	0.0, 1.0
$Ni(DIBM)_2$	4 hr.	84.0, 83.0	10.2, 6.7	5.8, 10.3
NaDIBM	1 hr.	82.3, 76.5	5.1, 12.0	12.6, 11.5
$Ba(DIBM)_2$	10 min.	84.7, 87.5	7.7, 7.5	7.6, 5.0
$Zn(DIBM)_2$	4 hr.	15.6, 20.2	33.8, 32.4	50.6, 47.5
$Hg(DIBM)_2$	6 hr	9.2, 12.6	73.0, 52.5	17.8, 34.9
$Cu(BIBM)_2$	16 hr.	45.6, 49.5	27.6, 19.9	26.8, 30.6
$Ni(BIBM)_2$	45 min.	45.0, 40.8	55.0, 38.2	0.0, 21.0
NaBIBM	40 min.	68.2, 68.0	31.8, 32.0	0.0, 0.0
$Ba(BIBM)_2$	15 min.	42.6, 41.0	20.6, 17.6	36.8, 41.4
$Zn(BIBM)_2$	1 hr.	28.3, 28.5	47.9, 44.5	23.8, 27.0
$Hg(BIBM)_2$	7 hr.	23.2, 21.6	20.4, 25.4	56.4, 53.0
$Cu(DBM)_2$	24 hr	32.1, 31.2	18.7, 22.0	49.2, 46.8
$Ni(DBM)_2$	2 hr.	31.5, 30.2	15.5, 11.8	53.0, 58.0
NaDBM	2 hr.	48.1, 46.3	24.3, 15.1	27.6, 38.6
$Ba(DBM)_2$	3 hr.	35.3, 36.2	58.2, 26.4	6.5, 37.4
$Zn(DBM)_2$	4 hr.	21.3, 22.6	24.0, 43.4	54.7, 34.0
$Hg(DBM)_2$	6 hr.	16.8, 19.7	0.0, 22.1	83.2, 58.2

Chelate	Reaction Time	% C-	% O-	% DK
$Cu(BnBM)_2$	8 hr.	32.5, 28.3	30.7, 30.6	36.8, 41.1
$Ni(BnBM)_2$	20 min.	44.6, 44.2	22.8, 26.8	32.6, 29.0
NaBnBM	20 min.	41.0, 38.4	38.8, 19.9	20.2, 41.7
$Be(BnBM)_2$	15 min.	30.6, 34.5	14.5, 44.4	54.9, 21.1
$Zn(BnBM)_2$	30 min.	12.8, 12.6	17.2, 42.0	70.0, 45.4
$Hg(BnBM)_2$	4 hr.	6.5, 9.0	59.5, 54.9	34.0, 36.1
$Cu(DnBM)_2$	2 hr.	34.5, 34.6	21.4, 43.1	44.1, 22.4
$Ni(DnBM)_2$	5 min.	35.1, 35.5	29.9, 41.0	35.0, 23.5
NaDnBM	5 min.	42.8, 41.0	40.0, 30.4	17.2, 28.6
$Be(DnBM)_2$	inst.	35.8, 35.5	48.7, 38.7	15.5, 25.8
$Zn(DnBM)_2$	3.5 hr.	0.0, 0.0	22.8, 41.9	77.2, 58.1
$Hg(DnBM)_2$	6.5 hr.	0.0, 0.0	74.1, 72.0	25.9, 28.0

(b) With Anisoyl Chloride in Cyclohexane.

Chelate	Reaction Time	%C-	%O-	% DK
$Cu(BnBM)_2$	10 hr.	5.0, 6.0	39.8, 44.2	55.2, 49.8
$Ni(BnBM)_2$	2 hr.	6.0, 7.0	23.5, 36.0	70.5, 57.0
NaBnBM	2 hr.	15.5, 12.1	23.0, 26.4	61.5, 61.5
$Zn(BnBM)_2$	inst.	5.5, 7.1	61.2, 49.0	33.3, 43.9
$Cu(DBM)_2$	24 hr.	2.0, 0.0	46.3, 68.1	51.7, 31.9
$Ni(DBM)_2$	2 hr.	0.0, 2.1	71.1, 55.1	28.9, 42.8
NaDBM	2 hr.	12.9, 10.1	37.0, 42.5	50.1, 48.4
$Zn(DBM)_2$	inst.	35.3, 31.8	62.4, 33.0	2.3, 35.2

(c) With p-Nitrobenzoyl Chloride in Cyclohexane.

Chelate	Reaction Time	% C-	% O-	% DK
$Cu(BnBM)_2$	inst.	81.6, 79.5	0.9, 2.8	17.5, 17.7
$Ni(BnBM)_2$	inst.	82.5, 80.2	0.0, 0.0	17.5, 18.8
NaBnBM	inst.	86.1, 84.0	2.1, 10.6	11.8, 5.4
$Zn(BnBM)_2$	30 min.	79.0, 82.0	8.1, 7.9	13.9, 10.1
NaDBM	10 min.	80% C- isolated		
$Cu(DIBM)_2$	30 min.	92% C- isolated		
NaDIBM	inst.	92% C- isolated		

(d) Reactions of the chelates in different solvents.

Chelate	Solvent	t	% C-	% O-	% DK
$Cu(DIBM)_2$	Et.Ac	6 hr.	37.0, 41.6	14.0, 33.2	49.0, 25.2
	MeCOEt	-	19.3, 10.5	32.3, 29.9	48.4, 60.6
Na(DIBM)	Et.Ac	inst	84.3, 79.5	15.7, 17.0	0.0, 3.5
	MeCOEt	inst.	79.9, 77.9	16.3, 18.6	3.8, 3.5
$Ba(BIBM)_2$	Et.Ac	inst.	45.5, 43.0	18.8, 19.0	35.7, 38.0
$Cu(DBM)_2$	Et.Ac	30 hr.	40.6, 38.2	0.0, 26.1	59.4, 35.7
	DMC	20 hr.	42.6, 36.8	20.8, 20.5	36.8, 42.7
$Ni(DBM)_2$	Et.Ac	inst.	52.4, 54.1	30.1, 30.4	17.9, 15.5
	DMC	3 hr.	54.6, 49.4	21.8, 23.3	23.6, 27.3
NaDBM	Et.Ac	inst.	68.0, 72.0	12.8, 12.4	19.2, 15.6
	DMC	inst.	63.5, 63.4	20.1, 20.6	16.4, 16.0
$Ba(DBM)_2$	Et.Ac	5 min.	57.5, 60.2	19.2, 16.5	23.3, 24.3
NaBnBM	Et.Ac	inst.	42.7, 42.5	36.6, 15.0	20.7, 42.5

(e) With benzoyl chloride in cyclohexane at room temperature.

Chelate	Reaction Time	% C-	% O-	% DK
NaBnBm	20 hr	63.6, 65.5	29.0, 29.5	7.4, 5.0
$Ba(BnBM)_2$	24 hr	39.5, 38.4	14.4, 36.6	46.1, 25.0
$Ni(BnBM)_2$	48 hr.	45.8, 44.2	9.6, 17.5	44.6, 38.3
$Zn(BnBM)_2$	72 hr.	48.0, 41.0	0.0, 21.1	52.0, 37.9
NaDBM	100 hr.	61.5, 62.6	26.4, 26.0	12.1, 11.4
$Ba(DBM)_2$	100 hr.	53.3, 52.3	27.3, 26.4	19.4, 21.3

Copper Di-isobutyroylmethane and Benzoyl Chloride. - Copper di-isobutyroylmethane (0.64 g.) and benzoyl chloride (0.483 g.) in cyclohexane (30 c.c.) were refluxed for 15 hr. and the reaction mixture was then treated as described above. The final solution, after ultraviolet analysis, was concentrated giving benzoyldi-isobutyroylmethane, (0.82 g. 90%) m.p. and mixed m.p. 86°, as white prisms. The inorganic residue from the reaction was cuprous chloride.

Nickel Di-isobutyroylmethane and Benzoyl Chloride. - Nickel di-isobutyroylmethane (2 g.) and benzoyl chloride (1.3 c.c.) were refluxed for 4.5 hr. in cyclohexane (100 c.c.). The final solution, obtained by treatment as above,

on concentration gave benzoyldi-isobutyroylmethane (2.42 g. 86%), m.p. and mixed m.p. 86°. The mother liquors, on treatment with a saturated solution of cupric acetate, gave copper di-isobutyroylmethane (0.16 g. 8% diketone), m.p. and mixed m.p. 123-124°.

Sodium Di-isobutyroylmethane and Benzoyl Chloride. - A mixture of sodium di-isobutyroylmethane (1 g.) and benzoyl chloride (0.65 c.c.) were refluxed for 1 hr. in cyclohexane (50 c.c.). The final solution, obtained as above, gave benzoyldi-isobutyroylmethane (1.17 g. 80%) m.p. 86° as white prisms. A trace of copper di-isobutyroylmethane was obtained by treating the mother liquors of the reaction with saturated cupric acetate solution.

Barium Di-isobutyroylmethane and Benzoyl Chloride. - Barium di-isobutyroylmethane (1 g.) and benzoyl chloride (0.54 c.c.) were refluxed for 5 min. in cyclohexane (50 c.c.) After treatment as above, the final solution was concentrated giving benzoyldi-isobutyroylmethane (0.93 g. 80%) m.p. 86°. A trace of copper di-isobutyroylmethane, m.p. 124° was isolated on treating the mother liquors with saturated cupric acetate solution.

Mercury Di-isobutyroylmethane and Benzoyl Chloride. - A suspension of mercury di-iosbutyroylmethane (0.36 g.) in cyclohexane (20 c.c.) was refluxed for 6.5 hr. with benzoyl chloride (0.17 c.c.). During the reflux the mixture became homogeneous. The final solution obtained as above was evaporated to dryness giving a yellow oil which was chromatographed on alumina. Petroleum ether eluted O-benzoyl di-isobutyroylmethane (0.22 g. 60%) identified by infrared comparison. The material did not give a colour with ferric chloride solution. Ether eluted traces of di-isobutyroylmethane identified by formation of the copper chelate, m.p. 123-124°. No trace of benzoyldi-isobutyroylmethane was eluted from the chromatogram.

Copper Di-isobutyroylmethane and p-Nitrobenzoyl Chloride. - Copper di-isobutyroylmethane (1.37 g.) in cyclohexane (100 c.c.) was refluxed for 30 min., with p-nitrobenzoyl chloride (1.15 g.). The mixture was then filtered, and the solvent evaporated off, giving p-nitrobenzoyl di-isobutyroylmethane (2.08 g., 92%), m.p. 104° as white needles, recrystallised from ether. (Found: C,62.54, H,6.36, N,4.56. $C_{18}H_{23}NO_5$ requires C,62.94, H,6.27, N,4.59%). λ max. 208 (ε,12,000) and 268 mμ (ε,20,500), ν max. 1660 (C:O) and 1600 cm.$^{-1}$ (aromatic).

Repetition of the above at room temperature. - A mixture of copper di-isobutyroylmethane (1.36 g.) and p-nitrobenzoylchloride (1.36 g.) in cyclohexane (70 c.c.) was allowed to stand for 24 hr. The reaction mixture was then filtered, and the organic solution concentrated giving p-nitrobenzoyldi-isobutyroylmethane (1.9 g. 86%), m.p. and mixed m.p. 103-104° as white needles. The inorganic product of reaction was proved to be mainly cupric chloride, by its solubility in water.

Sodium Di-isobutyroylmethane and p-Nitrobenzoyl Chloride. - A solution of sodium di-isobutyroylmethane (0.33 g.) in cyclohexane was refluxed for 5 min. with p-nitrobenzoyl chloride (0.35 g.). The reaction mixture was filtered hot, and the filtrate concentrated by distillation giving p-nitrobenzoyl di-isobutyroylmethane (0.52 g., 92%) m.p. and mixed m.p. 104°. No other product could be isolated.

Reaction of Copper Di-isobutyroylmethane with Benzoyl Chloride in presence of Pyridine. - Copper di-isobutyroylmethane (2.1 g. 0.0056 moles) was refluxed for 50 hr. with benzoyl chloride (4.3 c.c., 0.04 moles) in cyclohexane (100 c.c.) to which pyridine (0.45 g., 0.006 moles) had been added. On filtering the reaction mixture, no

inorganic product was isolated, and the organic substrate was still blue. The cyclohexane solution was washed with water, dilute hydrochloric acid and sodium bicarbonate solution, dried and concentrated giving copper di-isobutyroylmethane (1.6 g.), m.p. and mixed m.p. 123-124°. No evidence of any reaction could be obtained.

Reaction of Nickel Di-isobutyroylmethane with Benzoyl Chloride in presence of Pyridine. - Nickel di-isobutyroylmethane (2 g., 0.0055 moles) was refluxed for 48 hr. with benzoyl chloride (4 c.c.) 0.0035 moles) in cyclohexane (100 c.c.) to which pyridine (0.85 g., 0.011 moles) had been added. Once again there was no sign of reaction, and on treating as above, nickel di-isobutyroyl methane (1.3 g.), m.p. and mixed m.p. 170-172° was isolated.

Copper Benzoylisobutyroylmethane and Benzoyl Chloride. - Benzoyl chloride (1.08 c.c.) was added to a refluxing solution of copper benzoylisobutyroylmethane (2.05 g.) in cyclohexane and the mixture was refluxed for 16 hr. The final solution obtained as above was concentrated giving a

yellow gum, from which dibenzoylisobutyroylmethane (1 g. 40%) m.p. 135-136° was isolated on treatment with ether and petroleum ether. The mother liquors of the reaction were chromatographed on alumina. The initial fractions eluted with petroleum gave 3-benzoyloxy-4-methyl-1-phenyl-pent-2-ene-1-one (trace), m.p. 59-61°. Identity was confirmed by infrared comparison. Ether eluted traces of benzoylisobutyroylmethane identified by conversion to the copper chelate.

Sodium Benzoylisobutyroylmethane and Benzoyl Chloride.- A solution of sodium benzoylisobutyroylmethane (2.0 g.) in cyclohexane (100 c.c.) was refluxed for 40 min. with benzoyl chloride (1.1 c.c.). The reaction was treated as above and dibenzoylisobutyroylmethane (1.2 g.), m.p. 133-136° was isolated from the final solution. Chromatography of the mother liquors gave a trace of 3-benzoyloxy-4-methyl-1-phenyl-pent-2-ene-1-one, m.p. 56-59° from the fractions eluted with petroleum ether.

Zinc Benzoylisobutyroylmethane and Benzoyl Chloride. - A mixture of zinc benzoylisobutyroylmethane (3.25 g.) and benzoyl chloride (1.7 c.c.) in cyclohexane (160 c.c.) was refluxed for 1 hr. The final solution obtained as above was concentrated giving a yellow gum, from which 3-benzoyloxy-4-methyl-1-phenyl-pent-2-ene-1-one (1.4 g. 32%), m.p. 60-61°

crystallised. Further treatment of the gum with ether gave a solid m.p. 126-136° which, from infrared spectral evidence, was identified as a mixture of dibenzoylisobutyroylmethane, and 3-benzoyloxy-4-methyl-1-phenyl-pent-2-ene-1-one (0.6 g.).

Barium Benzoylisobutyroylmethane and Benzoyl Chloride.- A solution of barium benzoylisobutyroylmethane (2.1 g.) in cyclohexane (100 c.c.) was refluxed with benzoyl chloride (0.95 c.c.) for 20 min. The final solution obtained as above was concentrated giving, on fractional crystallisation, dibenzoylisobutyroylmethane (0.85 g. 35%) m.p. 130-136°.

Sodium Dibenzoylmethane and Benzoyl Chloride. - A suspension of sodium dibenzoylmethane (0.83 g.) in cyclohexane (42 c.c.) was refluxed for 2 hr. with benzoyl chloride (0.39 c.c.) the mixture being treated as above. The final solution was concentrated giving white needles of tribenzoylmethane (450 mg., 43%), m.p. 245°. Dibenzoylmethane was isolated from the mother liquors as its copper derivative (0.2 g., 22% diketone). No O-benzoyl dibenzoylmethane was isolated.

Nickel Dibenzoylmethane and Benzoyl Chloride. - Nickel dibenzoylmethane (1.48 g.) in cyclohexane (75 c.c.) was refluxed for 2 hr. with benzoyl chloride (0.67 c.c.) and

the reaction was then treated as above. The final solution obtained was concentrated giving a yellow solid (1.2 g.), m.p. 90-120°, which gave tribenzoylmethane (0.35 g. 20%) and a yellow gum on treatment with petroleum ether. This gum, on standing, gave crystals of O-benzoyl dibenzoylmethane (trace) m.p. 105-108°. The combined mother liquors from the crystallisations, on shaking with saturated cupric acetate solution, gave copper dibenzoylmethane (0.3 g., 20%), m.p. 297°.

Copper Benzoyl-n-butyroylmethane and Benzoyl Chloride.- A solution of copper benzoyl-n-butyroylmethane (2.02 g.) in cyclohexane (100 c.c.) was refluxed for 8 hr. with benzoyl chloride (1.02 c.c.) and the mixture was treated as above. The final solution was concentrated and methanol was added giving dibenzoyl-n-butyroylmethane (0.6 g., 22%) m.p. 108-110° as fine white needles. Copper benzoyl-n-butyroylmethane (0.4 g., 17% diketone) was isolated from the mother liquors after treatment with saturated cupric acetate solution.

Sodium Benzoyl-n-butyroylmethane and Benzoyl Chloride. A solution of sodium benzoyl-n-butyroylmethane (1.88 g.) in dry cyclohexane (100 c.c.) was refluxed for 20 min. with benzoyl chloride (1.04 c.c.) and the reaction mixture was treated as above. Dibenzoyl-n-butyroylmethane (0.76 g.,

29%) m.p.108-110° was isolated on concentration of the reaction solution. Chromatography of the mother liquors gave 3-benzoyloxy-1-phenyl-hex-2-ene-1-one (0.45 g., 17%), m.p. 48-50° eluted by petroleum ether. Later fractions, eluted by ether gave traces of benzoyl-n-butyroylmethane, identified by conversion to the copper chelate, m.p. 132-134°

Mercury Benzoyl-n-butyroylmethane and Benzoyl Chloride.- A mixture of mercury benzoyl-n-butyroylmethane (1.8 g.) and benzoyl chloride (0.72 c.c.) in cyclohexane (90 c.c.) was refluxed for 4 hr. and was then treated as above. The final solution was concentrated giving a yellow-red gum, which could not be crystallised. The gum was therefore chromatographed on alumina the initial fractions eluted with petroleum ether giving 3-benzoyloxy-1-phenyl-hex-2-ene-1-one (0.7 g. 39%), m.p. 48-50°. The product gave slight colour with ferric chloride solution.

Zinc Benzoyl-n-butyroylmethane and p-Nitrobenzoyl Chloride. - A solution of zinc benzoyl-n-butyroylmethane (0.42 g.) in cyclohexane (22 c.c.) was refluxed for 30 min. with p-nitrobenzoyl chloride (0.36 g.). The final solution, obtained after treatment of the reaction as above, gave p-nitrobenzoylbenzoyl-n-butyroylmethane (0.4 g., 62%), m.p. 89-91° as yellow needles. A trace of copper benzoyl-n-

butyroylmethane, m.p. 133-134° was isolated from the mother liquors on addition of cupric acetate solution.

Nickel Benzoyl-n-butyroylmethane and p-Nitrobenzoyl Chloride. - p-Nitrobenzoylbenzoyl-n-butyroylmethane (2.5 g., 61%) was likewise isolated from the final solution obtained from the reaction of nickel benzoyl-n-butyroylmethane (2.7 g.) and p-nitrobenzoyl chloride (2.5 g.) as described on p. 175.

Copper Di-n-butyroylmethane and Benzoyl Chloride. - Copper di-n-butyroylmethane (6.3 g.) in cyclohexane (150 c.c.) was refluxed for 3 hr. with benzoyl chloride (4.75 c.c.). On treatment of the reaction mixture as above, a final solution was obtained, from which a yellow gum was isolated on concentration. This gum was chromatographed on alumina, and the initial fractions eluted with petroleum ether, were rechromatographed, the initial fractions from this second chromatogram giving O-benzoyl di-n-butyroylmethane (0.49 g., 5.5%) as a colourless oil, identified by infrared comparison with an authentic specimen. Benzoyldi-n-butyroylmethane (0.8 g., 9%) was isolated from the benzene fractions from the initial chromatogram as described on p. 177-8.

Zinc Chloride and 3-Benzoyloxy-4-methyl-1-phenyl-pent-2-ene-1-one. - Anhydrous zinc chloride (0.2 g.) was dissolved in cyclohexane together with 3-benzoyloxy-4-methyl-

-1-phenyl-pent-2-ene-1-one (0.25 g.). The mixture was shaken for 2 hr. and was then diluted with pyridine and water. The cyclohexane was washed with dilute hydrochloric acid, sodium bicarbonate solution and water, dried and submitted for ultraviolet analysis. The results obtained showed that 80% of the 3-benzoyloxy-4-methyl-1-phenyl-pent-2-ene-1-one had been hydrolysed to benzoyl-n-butyroylmethane.

Zinc Chloride and Dibenzoylisobutyroylmethane. - A similar experiment using zinc chloride (0.3 g.) and dibenzoylisobutyroylmethane (0.35 g.) was carried out. On treatment as above, the final solution was submitted for ultraviolet analysis. The results showed that only 2% of the starting material had been hydrolysed. On concentrating the final solution, dibenzoylisobutyroylmethane was isolated in 90% yield, m.p. and mixed m.p. 135-136°.

Hydrolysis of the O-acylated Diketones with Pyridine/Water. - O-Benzoyldi-isobutyroylmethane (0.2 g.) was dissolved in pyridine (30 c.c.) and a trace of water was added. This mixture was allowed to stand for 24 hr. Cyclohexane was then added, and the cyclohexane solution was washed with water, dilute hydrochloric acid, sodium bicarbonate solution and water, dried and submitted for ultraviolet analysis.

This showed that a partial (10%) hydrolysis of the starting material to di-isobutyroylmethane had occurred. On treatment as above both O-benzoyldi-n-butyroylmethane and O-benzoyldibenzoylmethane were partially hydrolysed (8% and 12% respectively).

Reaction of the C-Acylated Diketones with Pyridine/Water. - Dibenzoylisobutyroylmethane (0.3 g.) was dissolved in pyridine (25 c.c.) and a trace of water was added. The mixture was allowed to stand for 24 hr. and was subsequently treated as above. Ultraviolet analysis of the final solution obtained showed that no hydrolysis had occurred within the experimental error.

Similarly, neither tribenzoylmethane nor dibenzoyl-n-butyroylmethane was hydrolysed on being treated as above.

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Summary of Ph.D Thesis.

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SUMMARY.

PART I

The discovery of 4-n-butyl-3,5-dioxo-1,2-diphenyl-pyrazolidine (Phenylbutazone), and its therapeutic value in the treatment of rheumatoid arthritis, has instigated an extensive study of pyrazolidine derivatives in an attempt to obtain a drug with the physiological activity of phenylbutazone, but without its attendant toxicity. Synthesis of 3-imino-5-oxo-1,2-diphenylpyrazolidine, by condensation of ethyl cyanoacetate with hydrazobenzene or by treatment of chloroacetylhydrazobenzene with potassium cyanide, opened the route to a parallel series of compounds which could also have physiological activity. The 4-ethyl homologue was synthesised similarly, but the 4-n-butyl homologue (c.f. phenylbutazone) could not be obtained by these synthetic routes. Further synthetic routes, including the attempted reductions of 4-butylidine-3-imino-5-oxo-1,2-diphenyl pyrazolidine and 4-butyroyl-3-imino-5-oxo-1,2-diphenyl pyrazolidine also failed to produce the 4-n-butyl homologue.

Synthesis of 4-amino-3-imino-5-oxo-1,2-diphenyl-pyrazolidine, by reduction of the 4-isonitroso derivative, obtained by nitrosation of 3-imino-5-oxo-1,2-diphenylpyrazolidine, made possible the formation of condensed cyclic derivatives of the pyrazolidine. Condensation of the 4-amino derivative with ethyl chloroformate gave 4-carbethoxyamino-3-imino-5-oxo-1,2-diphenylpyrazolidine, which could not be cyclised to an iminazo-

pyrazolidine. Nitrosation of the 4-amino derivative gave 4-azo-3-imino-5-oxo-1,2-diphenylpyrazolidine. Condensation of the 4-amino derivative with carbonyl chloride gave 4-carboxyamino-3-imino-5-oxo-1,2-diphenylpyrazolidine, in preference to cyclisation to the iminazo-pyrazolidine. With glyoxal, the 4-amino derivative gave 5-oxo-1,2-diphenyl-3,4-pyrazino-pyrazolidine. The 4-amino derivative also self-condensed to give 2,3-5,6-di-(5-oxo-1,2-diphenylpyrazolidine-3,4)-pyrazine. With acetylacetone the 4-amino derivative gave 4-acetylaceton-amino-3-imino-5-oxo-1,2-diphenylpyrazolidine. Samples of some of the above materials were sent for testing for physiological activity, but as yet no results are available.

PART II

It has long been known that sodium 'salts' of β-diketones react with acylating agents to give triketones and enolate esters of the diketone. However, little or no quantitative work has been done in determining the factors which influence the proportion of the two products formed. In this study, a quantitative examination of the factors, which might be expected to exert a large measure of control on the product ratio, was carried out. It was shown that the metal ion in the chelate influences the product ratio, with metals which have a co-ordination number greater than that required for chelation, giving higher triketone to enolate ester ratios than those metals, whose

co-ordination number is that required for chelation. It was also shown that steric factors in the organic ligand affect the product ratio, with triketone formation being favoured, if the steric requirements of the diketone substituents are large, and enolate ester formation being favoured if such requirements are small. Further, it was shown that electronic influences associated with the ligand and the acylating agent also affect the product ratio. If the acylating agent in S_N1 in character and/or the diketone substituents are electron-withdrawing in character, enolate ester formation is favoured. Conversely, if the acylating agent is S_N2 in character and/or the diketone substituents are electron-donating in character, triketone formation predominates, all other influencing factors being equal. Finally, the influences of reaction media and temperature on the product ratio have been studied. It is apparent that triketone formation is favoured by an increase in the polarity of the solvent, and a decrease in the temperature of the reaction. Based on a historical development, and incorporating the above study, a reaction mechanism has been postulated, substantiated by a semi-quantitative measure of the rates of the reactions.