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STUDIES ON PYRROLE DERIVATIVES

(Thesis in candidature for degree of
M.Sc., (Dunelm), April, 1958).

by

Alan Queen, B.Sc., (Dunelm).



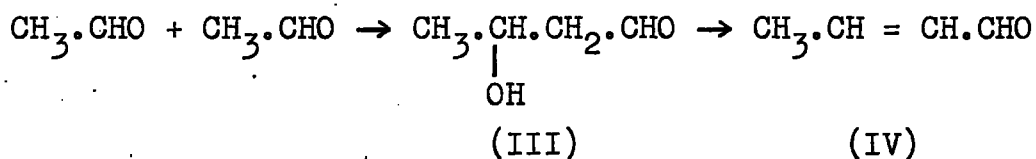
For convenience therefore this introduction is divided into five main sections, each dealing with a particular aspect of the published work. These divisions are:-

1. The reactions of aldehydes and ketones with active methylene groups. .
2. The reactions of cyanoacetamide with 1:3-diketones.
3. The reactions of cyanoacetamide with olefinic ketones and related compounds.
4. The structure of γ -ketoamides.
5. The reactions of 1:2-diketones with active methylene groups.

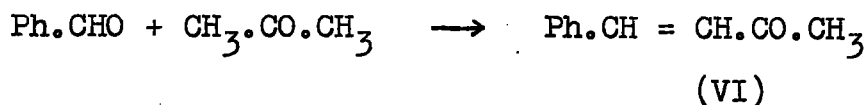
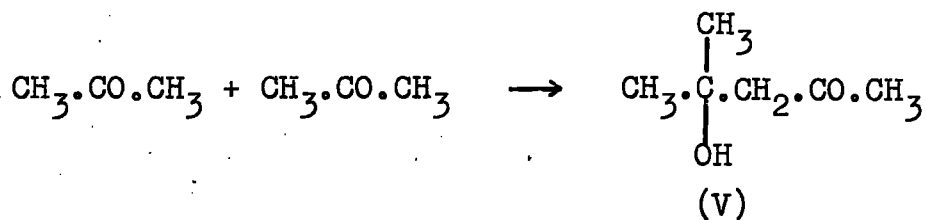
1. The reactions of aldehydes and ketones with active methylene groups

(a) Historical

Wurtz¹ discovered the self condensation of acetaldehyde to 3-hydroxybutyraldehyde (III) in the presence of hydrogen chloride or sodium bicarbonate, and later² demonstrated that it loses water on distillation to yield crotonaldehyde (IV).



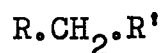
Subsequently³ caustic soda was introduced as a condensing agent, and since then other strong bases. For example, acetone condenses to diacetone alcohol (V) in the presence of barium hydroxide⁴. Frequently the aldol phase immediately loses water to give the unsaturated products directly. Thus, benzaldehyde and acetone give benzylidene acetone (VI)³ (compare Claisen³).



In the same way, benzaldehyde and ethyl acetate yield ethylcinnamate (VII) in the presence of sodium ethoxide⁵.



(VII)



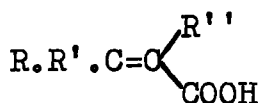
(VIII)

Malonic acid (VIII; R = R' = COOH), ethyl acetoacetate (VIII; R = CH₃CO, R' = COOEt) ethyl cyanoacetate (VIII; R = CN, R' = COOEt) and other compounds with two electrophilic substituents attached to the methylene group, react much more readily than simple aldehydes, ketones and esters. Knoevenagel⁶ found that ammonia and primary or secondary amines promote reaction with these compounds and ketones or aldehydes. In general compounds with such active methylene groups can cause ether mono- or di-substitution. Both classes of product will now be discussed.

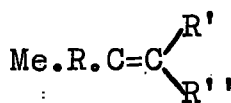
(b) Structures

(i) Mono-substitution products

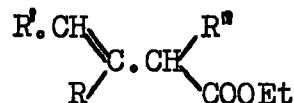
Aromatic aldehydes react with malonic acid in the presence of organic bases to give the α,β-unsaturated acids (IX; R = H, R' = Ph, R'' = H or COOH), depending upon whether or not carbon dioxide is eliminated^{6,7}.



(IX)

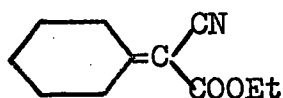


(X)

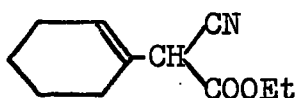


(XI)

Acetone and cyanoacetic ester (VIII; R = CN, R' = COOEt) in the presence of diethylamine give a mixture containing the cyano-ester (X; R = Me, R' = CN, R'' = COOEt)⁸. Similar products (X; R = H or alkyl, R' and R'' = CN, COOH, COOEt, NO₂, etc.) result by using, in the place of ethyl cyanoacetate, other compounds containing active methylene groups^{9,10,11}. When the chain length of the aldehyde or ketone exceeds three carbon atoms β,γ-unsaturated compounds (XI; R = H or alkyl, R' = alkyl or aryl, R'' = CN, COOEt, etc.) result as well, and may often constitute the main or sole product of the reaction. Thus, for example, phenylacetaldehyde and ethyl cyanoacetate give styryl cyanoacetic ester (XI; R = H, R' = Ph, R'' = CN) under the influence of diethylamine¹², and cyclohexanone yields a mixture of the α,β- and β,γ-olefinic products (XII) and (XIII) (7% and 93% respectively) when reacted with ethylcyanoacetate in the presence of sodium ethoxide^{13,14}.



(XII)



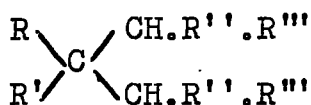
(XIII)

The effects of various bases on the condensation of aldehydes with malonic acid have been studied¹⁵. Whereas most bases give predominantly β,γ-unsaturated acids pyridine, which is most often used, gives mainly α,β-unsaturated

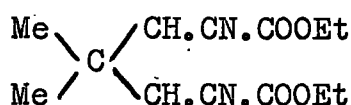
compounds and is therefore an atypical reagent.¹⁶

(ii) Disubstitution products

In addition to the unsaturated products described above, saturated compounds can also be obtained. These result either by direct reaction of the carbonyl compound with two molecules of the 'active methylene' compounds using the same bases, or by further reaction of the latter with an intermediate mono-substitution product. Compounds such as (XIV; R=H or alkyl, R' = alkyl, R'' and R''' = CN, COOH, COOEt, NO₂ etc.)^{6,11} form in this way. For example, acetone and ethyl cyanoacetate in the presence of diethylamine give (XV) (Komppa)⁸.



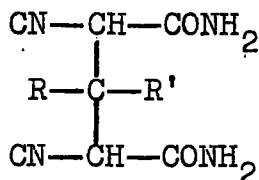
(XIV)



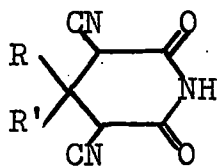
(XV)

Two special cases of these reactions occur between ketones or aldehydes and a) ethyl cyanoacetate in the presence of ethanolic ammonia, b) cyano acetamide under the influence of caustic soda or piperidine.

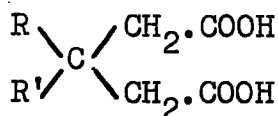
a) This reaction, developed by Guareschi¹⁷ and co-workers¹⁸ gives cyclic imides (XVII; R & R' = alkyl). These are presumably formed by loss of ammonia from the intermediates (XVI) in which the two cyano and two amido groups are cis as shown.



(XVI)



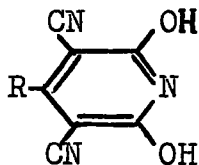
(XVII)



(XVIII)

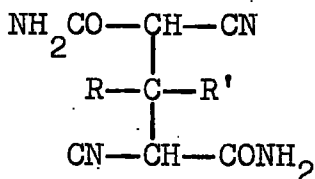
The structures of these products were proved by facile acid hydrolysis to β, β -disubstituted glutaric acids (XVIII; R and R' = alkyl).

The corresponding reaction with aldehydes leads to stable pyridine derivatives¹⁹ (XIX).

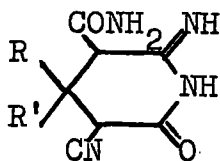


(XIX)

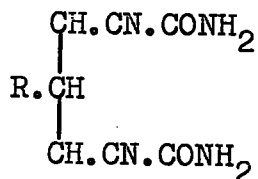
b) This reaction leads to cyclic imino-imides (XXI; R and R' = alkyl) when ketones are used^{20,21}. They are formed by the interaction of the cyano and amido groups in the trans intermediates (XX; R and R' = alkyl).



(XX)



(XXI)

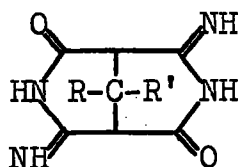


(XXII)

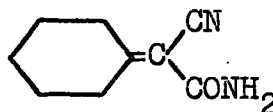
The imino-imides usually constitute the main products (95-98%) but small amounts of the imides (XVII) often result. Aldehydes give the open chain products^{22,23} (XXII; R = alkyl), which

in ethanolic solution with caustic soda or piperidine form the imino-imides (XXI; R = H, R' = alkyl).

The mono-imino-imides can be cyclised further, by cold sodium ethoxide, to di-imino-imides (XXIII; R = H, or alkyl, R' = alkyl). All of these products undergo acid hydrolysis to β -substituted glutaric acids.

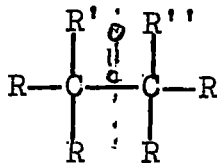


(XXIII)



(XXIV)

The compounds described above are generally the only products of the reaction of cyanoacetamide with aldehydes and ketones, but in a few cases^{21,23} unsaturated products, which react further with cyanoacetamide, have been isolated. For example, cyclohexanone forms (XXIV) by reaction with an equivalent of cyanoacetamide.

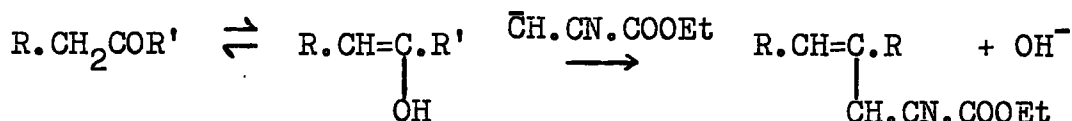


(XXV)

Disecundary ketones (XXV; R = alkyl, R' = R'' = H) react with cyanoacetamide giving poor yields of the above products, but if one of the substituents is tertiary (XXV; R = R' = alkyl, R'' = H) no reaction occurs (see Kon and Thorpe²¹).

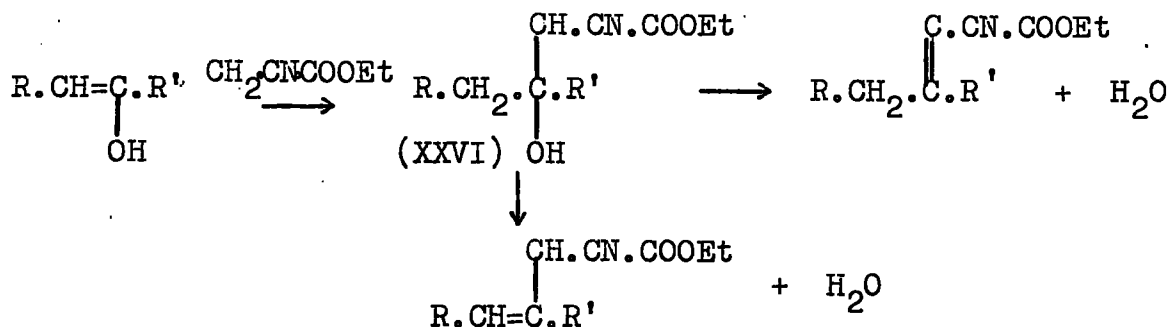
(c) Mechanisms

Early studies had revealed that an apparently essential factor for all these reactions was an enolisable ketone. The following mechanism was therefore assumed^{13,24} for the reaction of ketones with ethyl cyanoacetate, which reaction is typical of the whole series:-



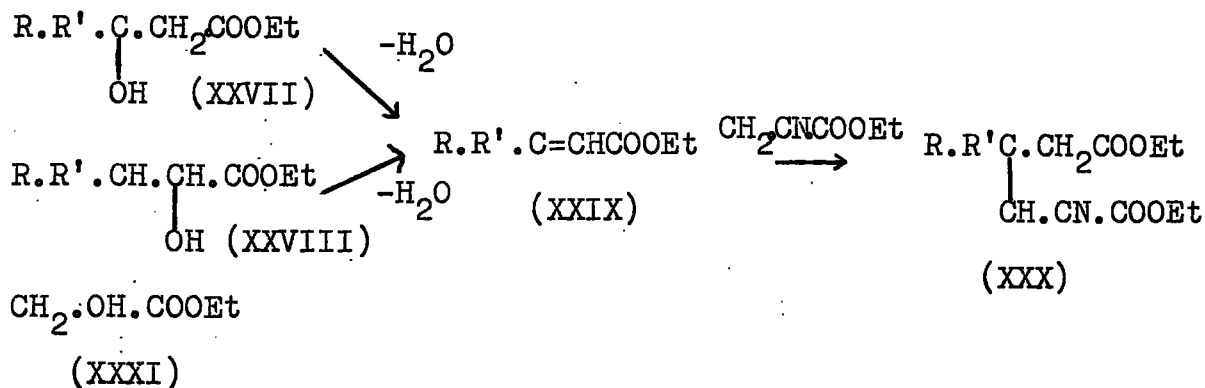
This mechanism explains satisfactorily the production of β,γ -unsaturated products but not of the α,β -isomers, which were usually attributed to a rearrangement of the former.

In 1921 Ingold¹⁴ pointed out a more plausible route involving addition to the double bond, and explaining the production of the α,β - as well as the β,γ -unsaturated form more convincingly by loss of water from the initial addition product (XXVI).

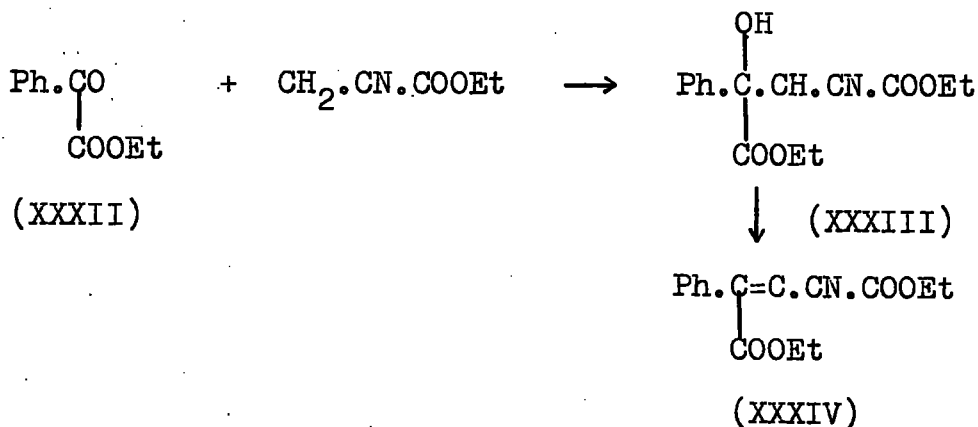


Ingold supported this mechanism by a study of the reactions of ethyl cyanoacetate with α - and β -hydroxy esters, (XXVII; R and R' = H or alkyl) and (XXVIII; R and R' = H or alkyl) respectively, in the presence of sodium ethoxide. The

products are all β -substituted cyanoesters (XXX; R and R' = H or alkyl), a result only understandable if the unsaturated intermediates (XXIX) are first formed, which then add sodio cyanoacetic ester:-

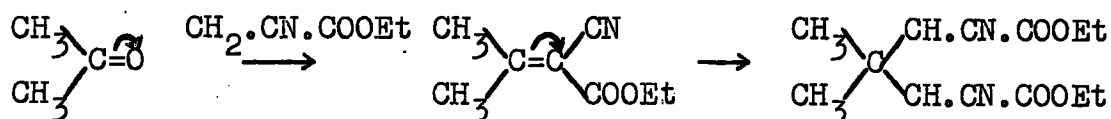


Glycollic ester (XXXI), which cannot lose a molecule of water to give an unsaturated intermediate, does not react. Later work by Corson and Kohler²⁵ casts doubt on the correctness of either mechanism, by showing that ethyl benzoyl formate (XXXII), which is incapable of keto-enol tautomerism, reacts with cyanoacetic ester, in the presence of most bases, to give the hydroxy product (XXXIII). This easily loses water to form the unsaturated cyano ester (XXXIV).



These facts led to the currently accepted mechanism²⁶ in which an aldol condensation occurs between ketones and aldehydes and active methylene groups, the initial adduct immediately losing a molecule of water in most cases to give unsaturated products.

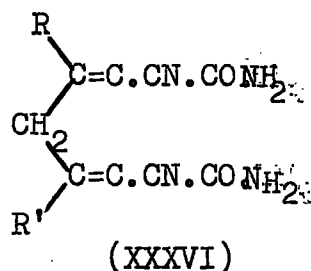
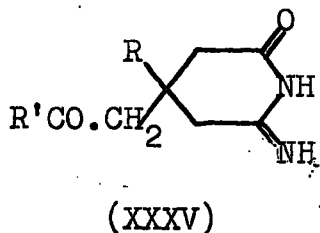
The formation of the disubstituted products has been assumed to proceed in two stages^{14,27}. In the first the unsaturated compounds described above are obtained. These then add a further molecule of the 'active methylene' compound to the double bond, under the influence of either sodium ethoxide (Michael addition) or piperidine (Knoevenagel addition). Using acetone and ethyl cyanoacetate as typical reagents the steps are:-



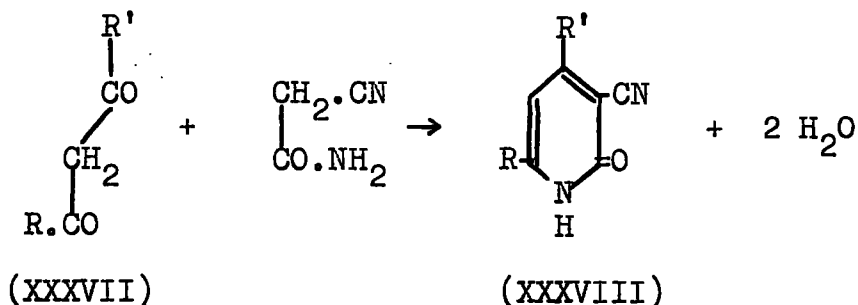
2. The reaction of cyanoacetamide with 1:3-diketones

(a) Structures

The presence of two keto groups in one of the reactants makes possible, in the light of the previous discussions, a large number of products. Thus to detail only two of them, reaction between two molecules of cyanoacetamide and one of diketone could lead to (XXXV) or (XXXVI).

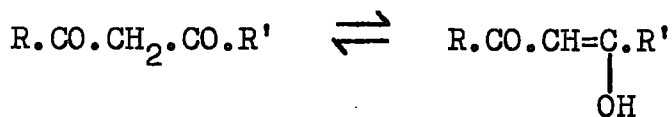


In fact reaction occurs between one molecule of each of the reactants with elimination of two molecules of water, under the influence of triethylamine²⁸ or piperidine²⁹. Aromatic³⁰ as well as aliphatic diketones react. The products are 3-cyano-4:6-disubstituted-2-pyridones (XXXVIII; R = alkyl or aryl, R' = alkyl, aryl or COOEt).



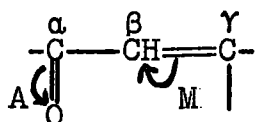
(b) Mechanism

With 1:3-diketones it is possible for both an enolic hydroxy- and a keto-group to be present at the same time:-



Both aldol and Michael (or Knoevenagel) additions are therefore possible. Ingold³¹ has in fact considered this problem and pointed out that one of these additions will probably predominate depending upon the electron dis-

placements in the molecule. Consider the system (XXXIX) and the ionisation of cyanoacetamide, which will be aided by bases:-

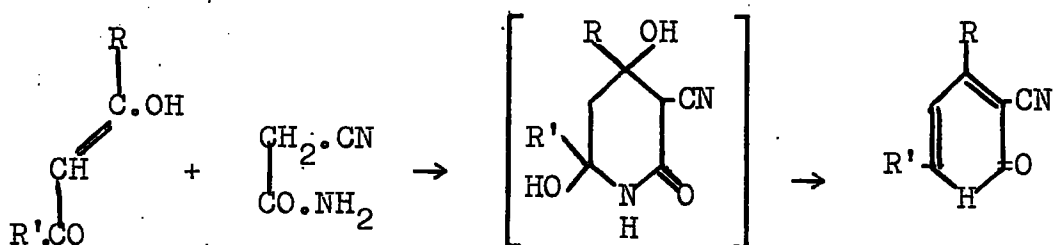


(XXXIX)

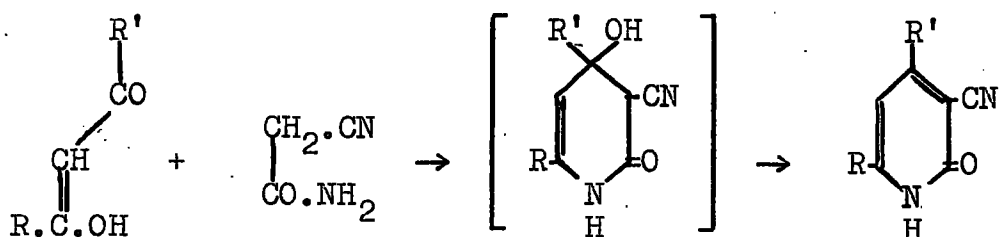


The symbols M and A stand for "Michael" and "Aldol" additions respectively, and the arrows indicate the direction of the electron migrations operative in each case.

If M is greater than A the Michael reaction will obviously be favoured and the cyanoacetamide anion will become attached to C γ , which in this case is the more positive centre. The mechanism is then:-

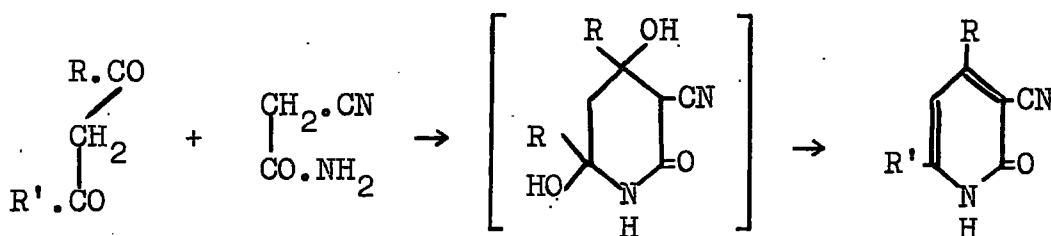


Similarly, if A is greater than M an aldol mechanism leads to attachment of the cyanoacetamide at C α . Thus:-



The orientation of the groups is different for each mechanism, but unfortunately the direction of enolisation is not fully established for unsymmetrical 1:3-diketones, and moreover the extent of M and A will be influenced by the adjacent groups R and R'.

Bardhan however²⁸ prefers the latter mechanism since with ethyl-2:4-dioxovalerate (XXXVII; R = Me, R' = COOEt), in which the enolism is plausibly in the direction of the 4-keto group, the product is the pyridone (XXXVIII; R = Me, R' = COOEt). However, an enolic form does not necessarily enter into the mechanism at all. An aldol addition at one keto group and interaction of the amido group with the other would lead to the following mechanism:-

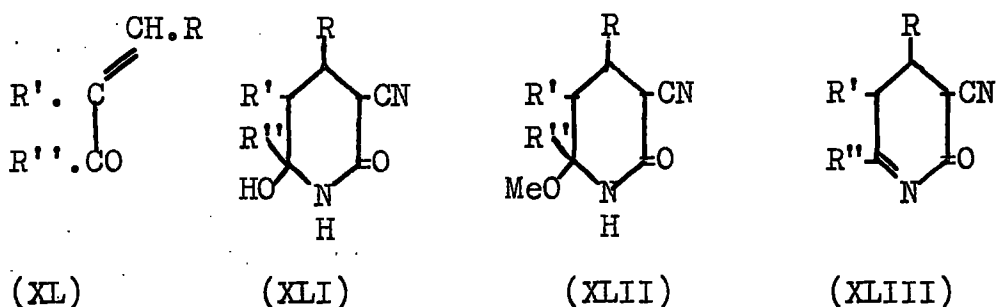


3. The reaction of cyanoacetamide with olefinicketones and related compounds

(a) α,β -Olefinic Ketones

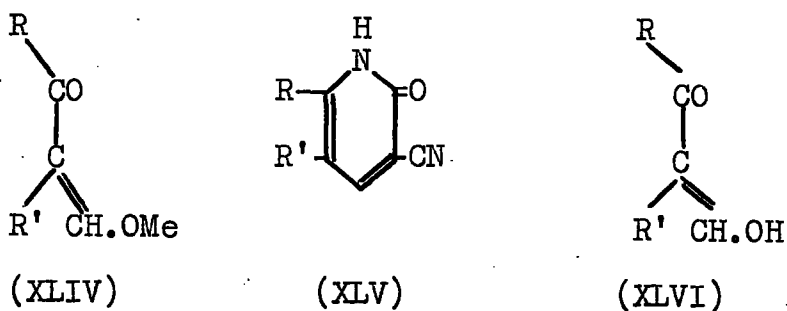
Cyanoacetamide reacts with α,β -unsaturated ketones (XL) in the presence of Michael's (sodium ethoxide) or Knoevenagel's (piperidine) catalysts³². With piperidine as

condensing agent hydroxypiperidones (XLI) result. These yield monomethyl derivatives (XLII) with methyl iodide, and in the presence of hydrogen chloride or hot acetic anhydride lose a molecule of water to form the unsaturated products (XLIII), which result directly when sodium ethoxide is used as the catalyst.



(b) Hydroxy- and methoxymethylene ketones

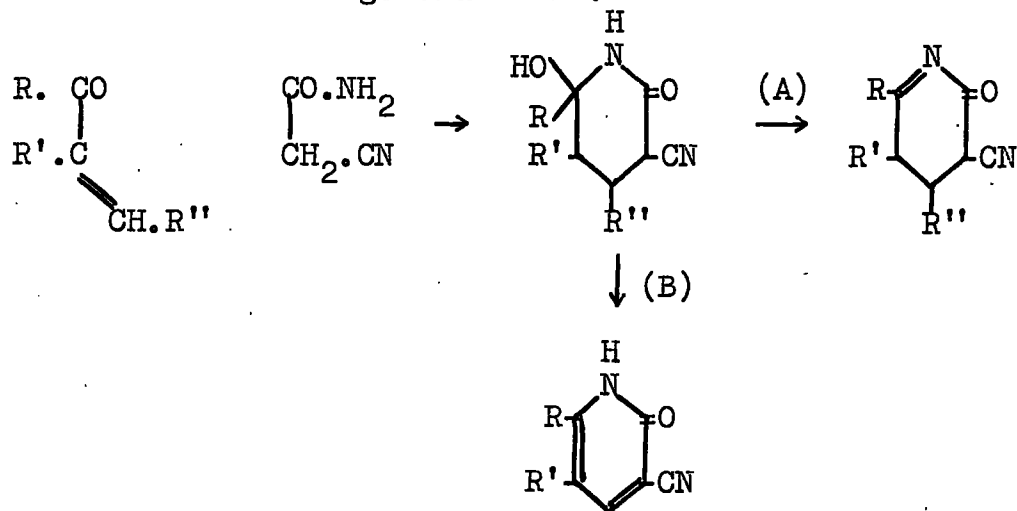
When methoxymethylene ketones (XLIV) react with cyanoacetamide in the presence of sodium ethoxide the methoxy group and a molecule of water are eliminated, to yield the pyridones (XLV)³³. Thus, methoxymethylene acetoacetic ester (XLIV; R = Me, R' = COOEt) and cyanoacetamide give 3-cyano-5-ethoxycarbonyl-6-methyl-2-pyridone (XLV; R = Me, R' = COOEt).



The corresponding reaction with hydroxymethylene ketones (XLVI) also gives the pyridones (XLV)³⁴.

(c) Mechanisms

The reactions described above have a feature in common: the methylene group of the cyanoacetamide reacts by addition to the double bonds, as is proved by the configuration of the products. The mechanisms therefore involve a Michael or Knoevenagel addition at this centre rather than an Aldol reaction with the keto group (see page 12 for a discussion of these reactions). The mechanisms can therefore be written in the general form:-



When R'' is OH or OMe loss of water (two molecules), or water and methanol, leads to the pyridones (XLV) (route B), but when R'' is alkyl, aryl or similar groups, loss of a molecule of water gives (XLIII) (route A).

^d
(b) Discussion

The implication of the results given in the previous pages is that α,β -olefinic bonds are more reactive towards active methylenes than are keto groups. It does not follow that this will invariably be so. Ingold et al.³⁵ have pointed out that alkyl and aryl groups adjacent to a double bond inhibit additions of the Michael and Knoevenagel types, and that the effect increases with the size of the group. Steric factors are probably involved as well as electronic effects. Strongly electrophilic substituents on the other hand, aid addition. The same groups have similar effects on the aldol reaction, for the obvious reason that they inhibit or promote, in the same way, the electron migrations necessary for the reactions to occur. When the substituents are all of one type these factors have little influence on the course of a reaction, but with dissimilar substituents become of great importance.

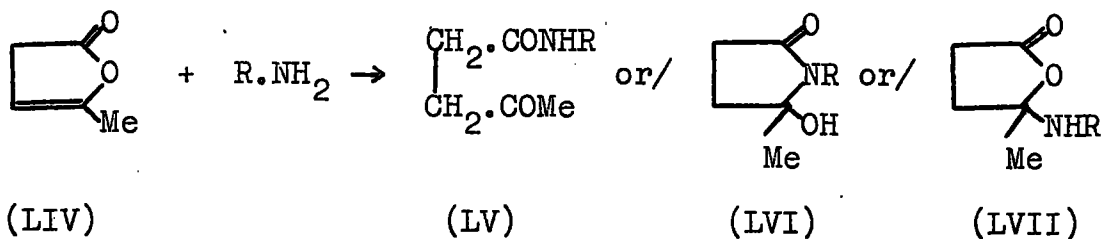
4. The structure of γ -ketoamides

(a) Historical

Beilstein³⁶ first suggested that γ -ketoamides may, due to interaction between the keto and amido groups, exist as cyclic compounds. In the case of levulinamide the three possibilities which must be considered are the open chain (XLVII), pyrrolidone (XLVIII) and furanone (XLIX),

The products lose water on reduced pressure distillation yielding unsaturated pyrrolones (LIII), a reaction reminiscent of Wolff's observation with levulinamide.

For comparative purposes they also prepared N-methyl levulinamide and levulinanilide by reacting a) methylamine, and b) aniline with angelica lactone (LIV).

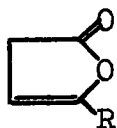


Three structures (LV; LVI; and LVII; R = Me or Ph) are possible for these products. On heating under reduced pressure loss of water occurs, a fact arguing against the furanone formulations (LVII). The N-methyl compound is an oil which reacts with aniline to yield a crystalline acid, whereas the pyrrolidone (LVI; R = R' = Me) is a solid unreactive towards aniline. The conclusion to be drawn from the quoted facts is that the two compounds are different. Similarly the anilide and N-phenyl-hydroxypyrrolidone (LVI; R = Ph, R' = Me) differ, since only the former gives a crystalline anil. Despite identical melting points for the above compounds, no mixed melting points are recorded.

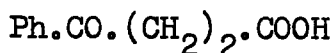
The pyrrolidone and furanone structures for N-methyl- and N-phenyl-levulinamide having thus been disproved, the compounds must be the open chain forms.

(ii) Evidence supporting the hydroxypyrrolidone formulation

Recently Walton³⁹ has criticised the above work and presented evidence that Lukes and Prelog had in fact obtained cyclic products from angelica lactone and amines. He reacted the lactones (LVIII; R = Me or Ph) with ammonia and primary amines and showed that the products are hydroxypyrrolidones, identical with the compounds obtained by reacting N-substituted succinimides with Grignard reagents (compare page 18).



(LVIII)



(LIX)

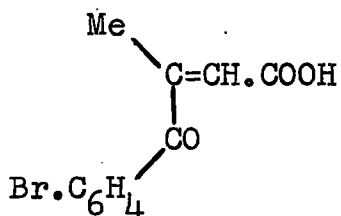
Thus γ -ketoamides are cyclic hydroxypyrrolidones. The properties of the compounds are in accord with this. They are amphoteric, a property unexpected in a simple ketoamide, and they are not easily hydrolysed by caustic soda, a fact which argues against the presence of a free amido group. The products from the above lactones and secondary amines must be open chain compounds, and in contrast to the

pyrrolidones are not amphoteric and easily yield β -benzoylpropionic acid (LIX) with hot caustic soda.

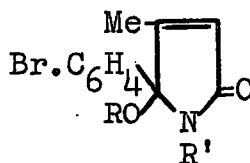
(c) α, β -Unsaturated γ -ketoamides

(i) The amides and anilides of β -p-bromobenzoyl crotonic acid (LX)

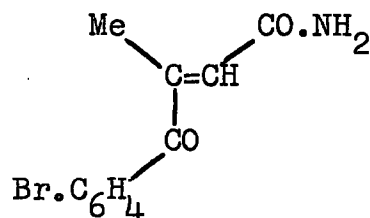
Recently⁴⁰ 5-hydroxypyrrolinones (LXI; R = H; R' = H, Me, or Ph) have been prepared by reaction of the chloride of the above acid with ammonia, methylamine and aniline. The presence of the allylic tertiary hydroxy group is demonstrated by the solubility of the compounds in dilute caustic soda, and by the formation of monomethyl ethers (LXI; R = Me, R' = H, Me, or Ph) on reaction with methanol and hydrogen chloride.



(LX)



(LXI)

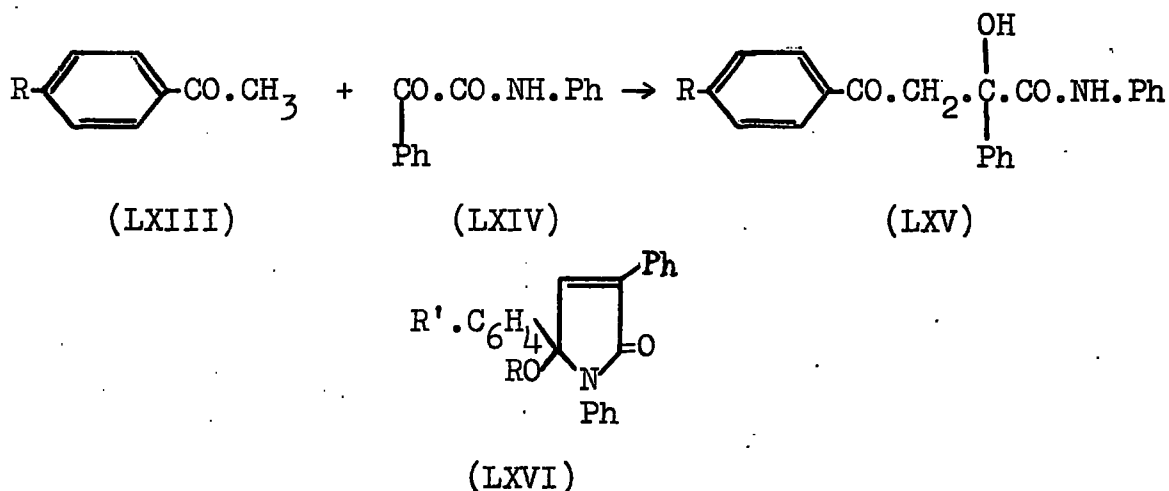


(LXII)

Reaction of the trans acid chloride with ammonia in the absence of ultra-violet light, leads to an isomeric amide with quite different properties. For example, it is insoluble in dilute caustic soda and does not yield a methyl derivative. It is the trans amide (LXII) and in the presence of light rapidly changes to the cyclic form.

(ii) Other hydroxypyrrolinones

The reaction of benzoylformanilide (LXIV) with the acetophenones (LXIII; R = H or Br) leads to open chain γ -ketoanilides (LXV; R = H or Br), which under the influence of hydrogen chloride lose a molecule of water and cyclise to the hydroxypyrrolinones (LXVI; R = H, R' = H or Br).



These, with ethanolic or methanolic hydrogen chloride, yield ethyl and methyl ethers (LXVI; R = Me, or Et, R' = H or Br). It appears therefore that the N-phenyl group gives some stability to the open chain γ -ketoanilides (LXV; R = H or Br), but the ease of cyclisation shows that the effect is not very pronounced.

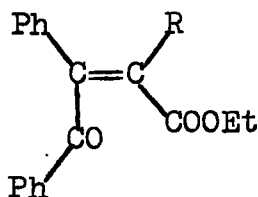
(d) Summary

The conclusion to be drawn from the work described in the preceding pages, is that in general γ -ketoamides are cyclic pyrrolidone and pyrrolinone derivatives. The ring

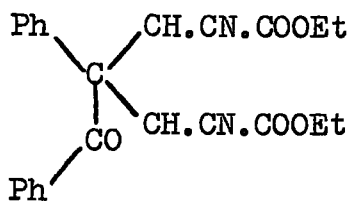
structure enhances the stability of the amido group, and the hydroxy group accounts for the weak acidity. Steric factors may confer some stability to an open chain form of some γ -ketoamides, and it has been observed that for two γ -ketoanilides (page 22) the N-phenyl group does so to some extent.

5. The Reaction of 1:2-diketones with active methylene groups

Very little attention has been devoted to such reactions. Benzil and ethyl malonate in the presence of sodium ethoxide give (LXVII; R = COOH)⁴², and the same diketone reacts with ethyl cyanoacetate under the influence of piperidine to give an excellent yield of the cyano-ester (LXVII; R = CN)⁴³. It is also claimed, without analytical evidence, that in the presence of a large excess of the base the latter reaction gives a small amount of the disubstitution product (LXVIII).



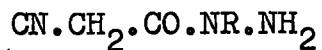
(LXVII)



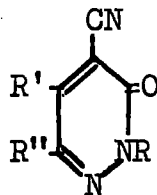
(LXVIII)

Although cyanoacetamide has not been reacted with 1:2-diketones it has been shown⁴⁴ that cyanoacetic hydrazides (LXIX) react with these diketones, under the influence of

bases, to give pyridazinones (LXX).



(LXIX)

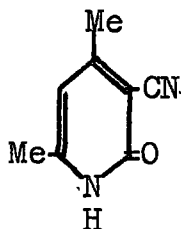


(LXX)

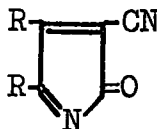
These reactions emphasise the tendency for six membered heterocyclic rings to form in preference to open chain compounds, and it remains to be seen whether or not five membered rings form in the same way from 1:2-diketones and cyanoacetamide.

THEORETICAL

This work is an investigation of the reactions between cyanoacetamide and 1:2-diketones. It was originally undertaken because of the likelihood that the reaction would follow a course similar to that for 1:3-diketones. Thus Bardhan²⁸ and Wagtendonk and Weiburg²⁹ have shown that acetylacetone and cyanoacetamide under basic conditions (triethylamine or piperidine) give 3-cyano-4:6-dimethyl-2-pyridone (I). By analogy the products from 1:2-diketones would be the pyrrolenones (II), which were in fact desired as intermediates.



(I)



(II)

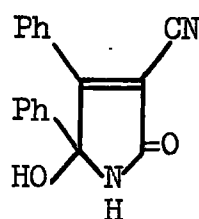
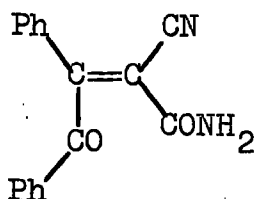
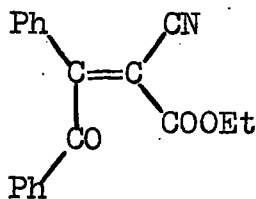
The reaction, however, takes a different course and in the following pages the structures and further reactions of the products are discussed. This discussion is divided into three sections as follows:-

1. Reaction of one molecule of cyanoacetamide with benzil.
2. Reaction of cyanoacetamide with aliphatic 1:2-diketones and with the pyrrolinone described in (I).
3. The glutaro-dilactones and attempts to synthesise them.

1. The reaction of one molecule of cyanoacetamide with benzil

When benzil reacts with cyanoacetamide under the influence of either piperidine or sodium ethoxide an excellent yield of a colourless crystalline solid results. This analyses as $C_{17}H_{14}O_3N_2$, a formula suggesting that addition has taken place between one molecule of the diketone and one of the cyanoacetamide. On recrystallisation from aqueous pyridine a molecule of water is lost and a further product is obtained, which also results by prolonged refluxing in a benzene solution. When this new compound is further recrystallised from aqueous ethanol the original product is recovered. These facts strongly suggest that the initial product isolates as a simple hydrate in which the water molecule is very loosely bound.

The above products also result from the reaction of ethyl 3-benzoyl-2-cyanocinnamate (III) and ethanolic ammonia under reflux. They must therefore be derived from 3-benzoyl-2-cyanocinnamamide (IV), and hence contain the α -cyano-cinnamoyl grouping.



Confirmation of these conclusions is obtained from the ultra-violet spectra of the two products. Coenen and Pestener⁴⁵ have shown that the α -cyano-cinnamoyl group gives a characteristic absorption maximum at about 290 μ . Both of the above compounds exhibit this peak, as does the ester (III), confirming the presence of the grouping in all three. Absorption data are listed in Table I (page 29).

Both the anhydride and hydrate are unreactive to hydroxylamine, semicarbazide and 2:4-dinitrophenylhydrazine. For these reasons the simple structure (IV) must be held in doubt. An alternative (V), in which the keto group is masked by interaction with the adjoining amide group to give a cyclic structure, has also to be considered.

The open chain form (IV) is only tenable if steric hindrance about the keto group can be established. To investigate this possibility ethyl 3-benzoyl-2-cyanocinnamate (III), synthesised by condensation between benzil and ethyl cyanoacetate in the presence of piperidine (cf. Bächer⁴³), has been subjected to a comparative examination. This ester does not yield either an oxime or a 2:4-dinitrophenylhydrazone under the usual conditions. This can only be due to steric hindrance, since in this case there is no way of masking the keto group. Because of the similarity between (III) and (IV) the latter structure would be expected to lack ketonic

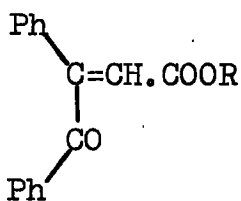
properties. Despite this, further work shows conclusively that (V) is in fact correct. The evidence for this is conveniently divided into (a) evidence for the absence of a keto group, and (b) evidence for the presence of a tertiary hydroxy group.

(a) Evidence for the absence of a keto group

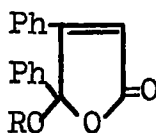
This evidence comes from spectral examination in the ultra-violet and infra-red regions.

(i) Ultra-violet spectra

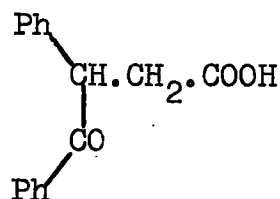
Some related compounds have already been examined in the ultra-violet between 200 and 300 μ . by Browne and Lutz⁴⁶ who have studied 3-benzoylcinnamic acid (VI; R = H) and its cyclic (VII; R = Me) and open chain (VI; R = Me) methyl esters. They have associated the free benzoyl group in these compounds and in 3-benzoyl-3-phenylpropionic acid (VIII), with a strong band near 245 μ . ($\epsilon_{\text{max.}} \approx 12,000$) and have shown that the cyclic structures (VII) do not exhibit this band, but show only a single cinnamoyl peak near 275 μ .



(VI)



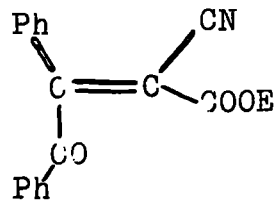
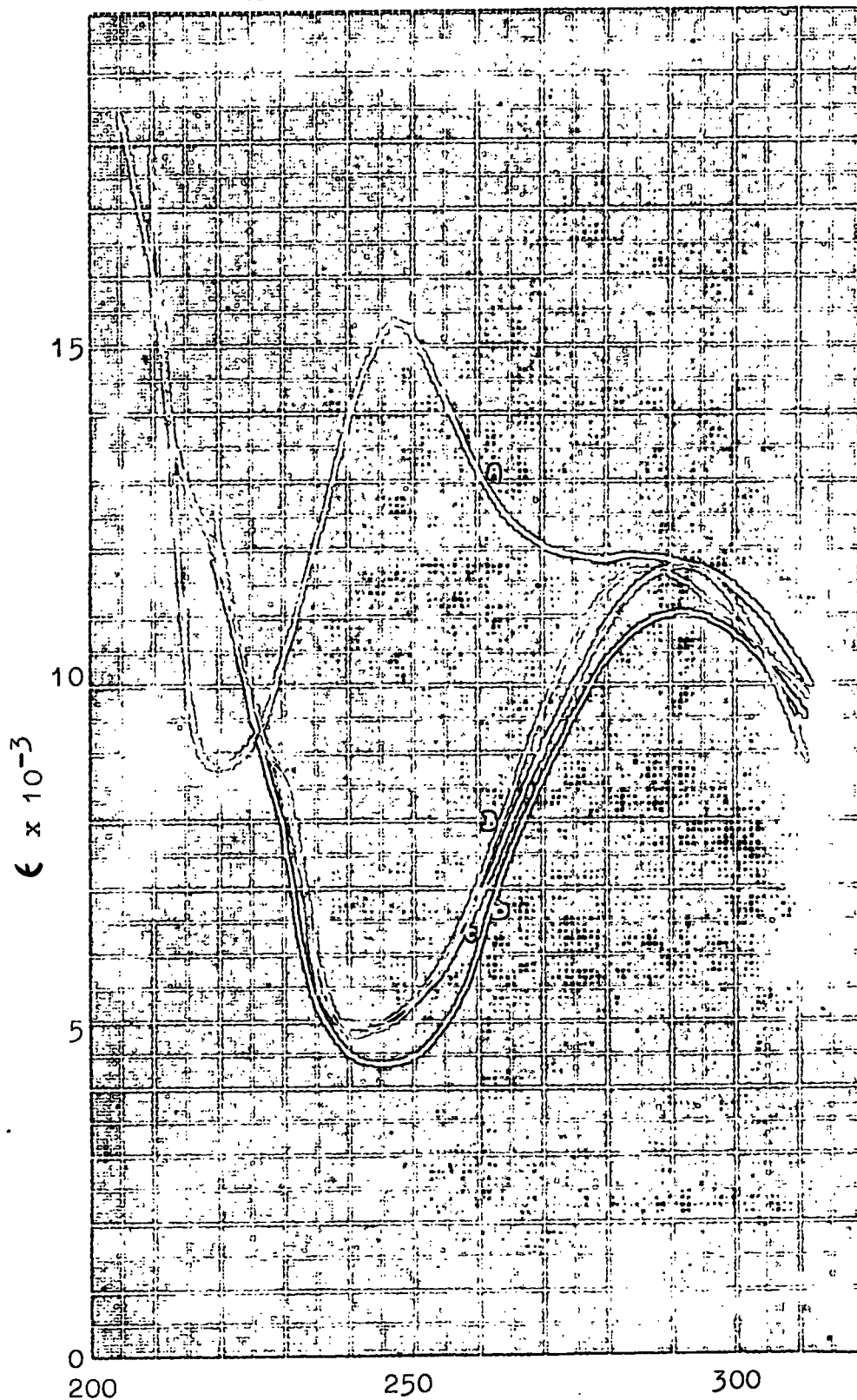
(VII)



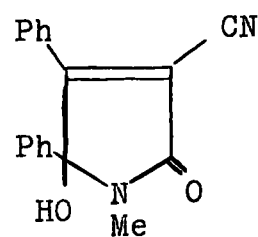
(VIII)

The spectrum of the cyanoester (III) in ethanol supports the

Ultra-violet Spectra (in ethanol).



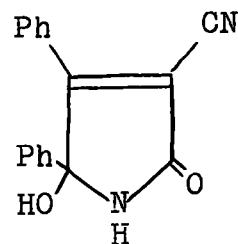
(A) —



(B) —

Hydrate.

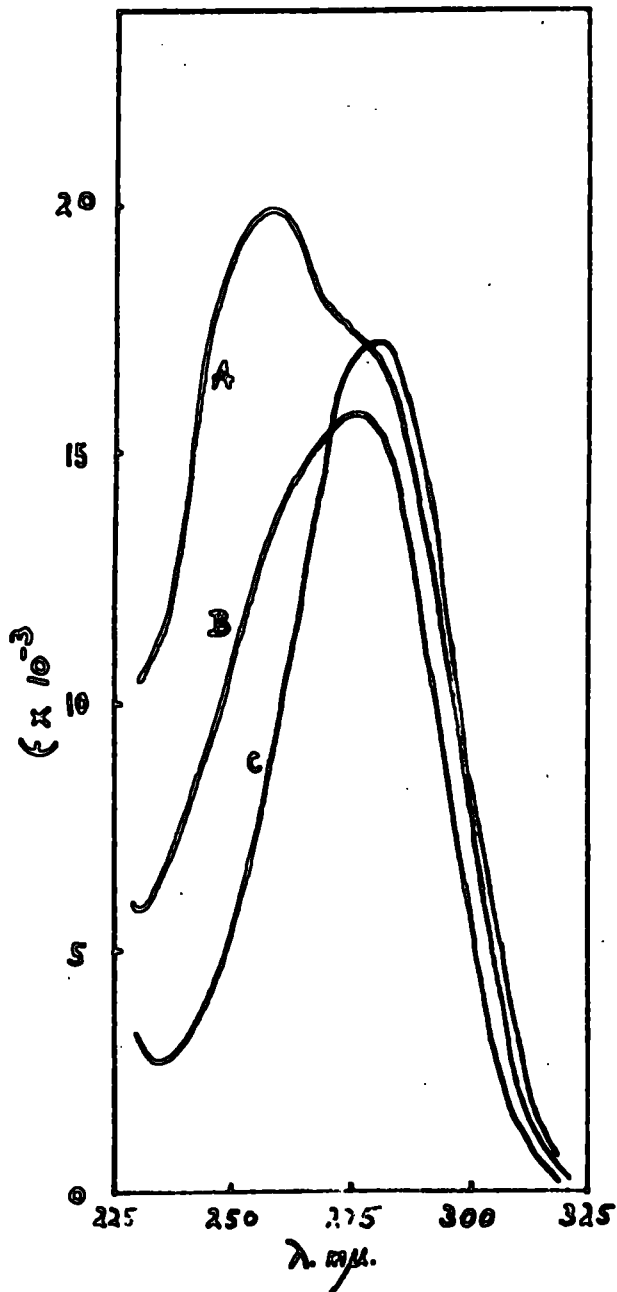
(C) —



(D)

Wavelength $m\mu$

Ultra-violet Spectra



3-Benzoylcinnamic acid derivatives (Browne & Lutz⁴⁶).

- A. Open chain methyl ester (VI; R=Me)
- B. Cyclic acid (VII; R=H)
- C. Cyclic methyl ester (VII; R=Me)

generality of these authors' work, as it shows the expected benzoyl and α -cyanocinnamoyl bands at 247 μ . and 285 μ . respectively.

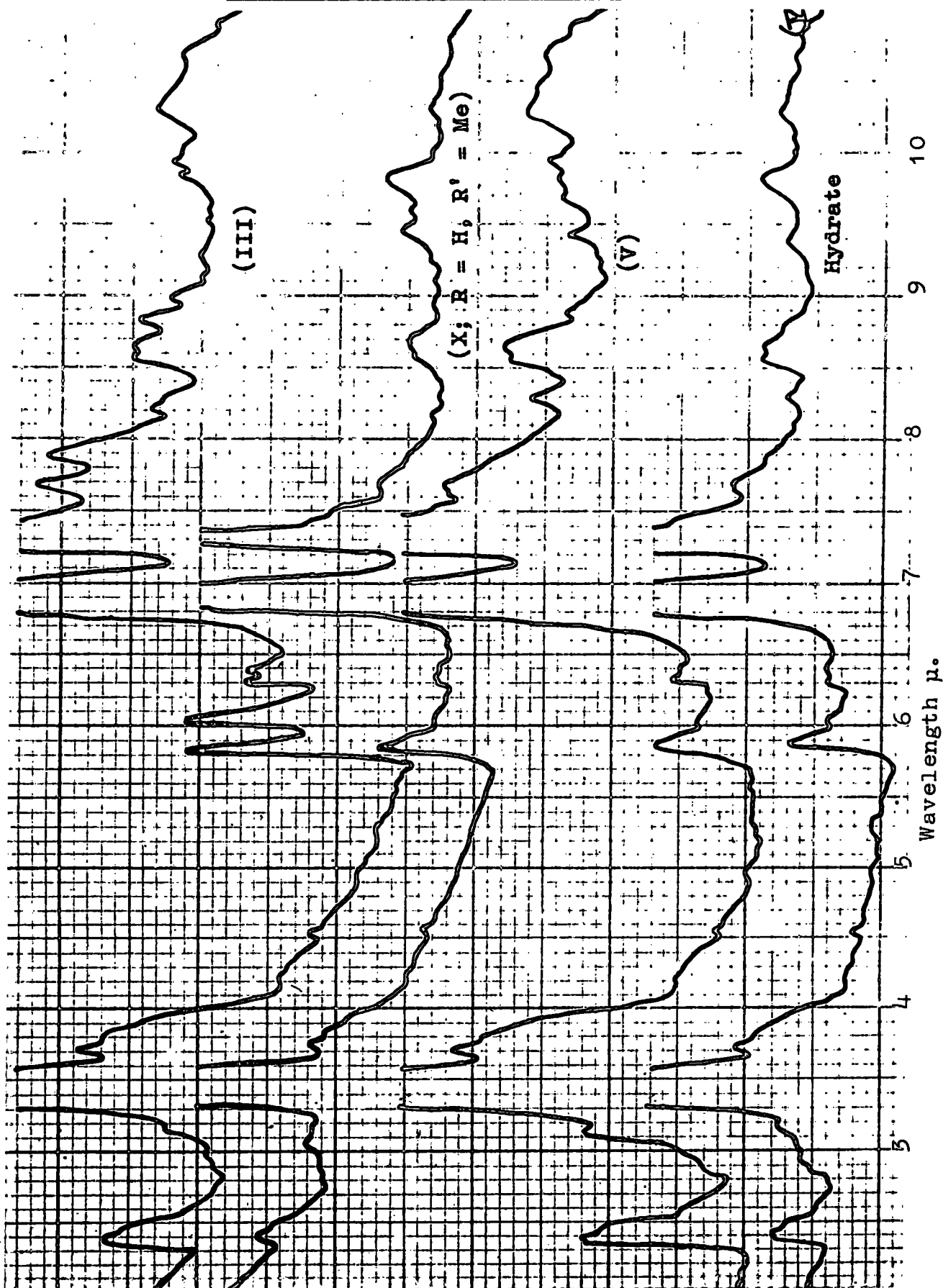
TABLE I
Ultra-violet absorptions

Compound	Cinnamoyl Band		Benzoyl Band	
	$\lambda_{\text{max.}}$	$\epsilon_{\text{max.}}$	$\lambda_{\text{max.}}$	$\epsilon_{\text{max.}}$
III	285	11,890	247	15,350
(V) hydrate	292	11,760	-	-
(V) anhydrous	293	11,043	-	-

(ii) Infra-red spectra

The infra-red spectra of the ester (III), the hydrate and the anhydride have been compared in the carbonyl region (5-6 μ .). While the ester shows two bands at 5.85 and 6.05 μ . the other two compounds each show only a single peak at 5.85 μ . It can be argued that the peak at 6.05 μ . for the ester is due to the benzoyl group that it admittedly contains, and that the suppression of this band in the cases of the hydrate and anhydride must indicate that neither contain such a centre. The 5.85 μ . bands can be plausibly assigned to the ester carbonyl in (III) and to a lactam carbonyl in the other compounds. The evidence for this is conveniently discussed at this point.

Infra-red Spectra (in nujol mull).

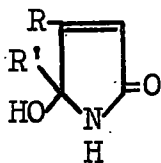


The primary amide group is well-known to show a pair of bands near 5.9 and 6.1 μ . The latter band is the so-called amide (II) band which originates in N-H stretching oscillations (cf. Bellamy⁴⁷ and Weissberger⁴⁸). The amide (II) band has usually about a third of the intensity of the amide (I) band. Lactams do not appear to exhibit this pair, but only the carbonyl frequency. As the bands at 5.85 μ . have not been resolved in the above compounds it must be held that the evidence from these spectra not only indicates the absence of a benzoyl group in the hydrate and anhydride, but also the presence of a lactam ring, and hence supports the ring structure (V).

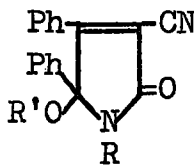
(b) Evidence for the presence of a tertiary hydroxy group

(i) Acidity

Both the hydrate and anhydride dissolve in cold dilute aqueous caustic soda, yielding yellow solutions from which the hydrate precipitates on acidification. Neither is soluble in sodium bicarbonate solution. This weak acidity is attributed to the presence of a tertiary hydroxy group, allylic to the double bond. Similar properties have been reported for 5-p-bromophenyl-5-hydroxy-4-methyl-2-pyrrolinone (IX; R = Me, R' = Br.C₆H₄) by Hill and Lutz⁴⁰.



(IX)



(X)

(ii) Ether formation

Reaction of either the hydrate or the anhydride with ethanol (or methanol) in the presence of dilute hydrochloric acid leads to the same water-free mono-ethyl (or -methyl) derivatives. As these products are not soluble in dilute alkali they cannot contain an allylic hydroxy group, a fact which points to their structures. They must be the O-ethers (X; R = H, R' = Me or Et). This is confirmed by a Zeisel determination on the methyl derivative.

In view of the weak acidity previously attributed to the allylic hydroxy group in the parent compounds, these derivatives may be regarded as pseudo esters.

The cyclic nature of the methyl derivative is further supported by its infra-red spectrum which exhibits a single band at 5.85 μ . which has been previously shown (page 29) to be best attributed to a lactam carbonyl.

These facts therefore support the pyrrolinone structure (V).

(iii) Action of dimethyl sulphate

With dimethyl sulphate in the presence of caustic

soda the hydrate (or the anhydride) yields a mixture of two products, a mono- and a dimethyl derivative. The 'mono' dissolves in dilute alkali whereas the 'di' is insoluble. This fact, which was used to separate the compounds, also indicates their structures. Thus the 'mono' must have a free allylic hydroxy group to account for its acidity. It is therefore a 1-methyl-5-hydroxy-2-pyrrolinone (X; R = Me; R' = H), whereas the 'di', which lacks the acidity, must be a 1-methyl-5-methoxy-2-pyrrolinone (X; R = R' = Me).

These deductions are confirmed by the results of Zeisel estimations. The cyclic nature of the mono-methyl derivative is also confirmed by its ultra-violet spectrum which shows a single α -cyano-cinnamyl band at 288 m μ .

($\epsilon_{\text{max.}}$ = 11,690).

(iv) The action of acetic anhydride

The hydrate (or the anhydride) reacts with acetic anhydride in pyridine under reflux to give a diacetate. This product is not soluble in cold dilute alkali and hence does not contain an allylic hydroxy group. It is therefore given the structure (X; R = R' = COCH₃). This derivative provides further evidence for the pyrrolinone formulation (V) in that it confirms the presence of two reactive centres.

The use of other acylating reagents, namely, acetyl, benzyl and p-toluene sulphonyl chlorides, does not

lead to either mono- or di- derivatives, no reaction occurring with these reagents.

(c) Recapitulation

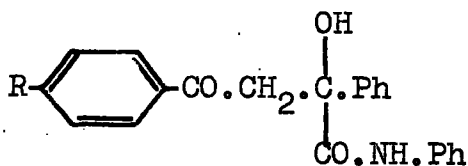
The condensation of benzil with one molecule of cyanoacetamide under the influence of piperidine leads to a monohydrate which easily loses water to give an anhydrous product $C_{17}H_{12}O_2N_2$. The same products result from the reaction of ethyl-3-benzoyl-2-cyanocinnamate (III) with boiling ethanolic ammonia. They must therefore contain the α -cyanocinnamoyl group, and are most probably derived from 3-benzoyl-2-cyanocinnamamide (IV).

Neither of the compounds react with hydroxylamine, semicarbazide or 2:4-dinitrophenylhydrazine. They therefore either do not contain a keto group, or this centre is masked by steric hindrance. Two structures (IV) and (V) are therefore indicated.

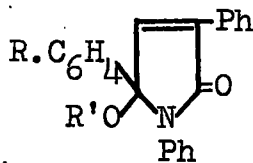
Support for the second of these alternatives comes from a study of the infra-red and ultra-violet spectra of the products. In the infra-red both absorb strongly only at 5.85μ . (in the carbonyl region), whereas the related keto-ester (III) has a further peak at 6.05μ . attributable to its benzoyl group. The ultra-violet spectra reveal only an α -cyanocinnamoyl band near $295 m\mu$. whereas (III) has in addition a benzoyl peak at $245 m\mu$. These facts can only be explained on the cyclic formulation (V).

Chemical evidence supports these views by showing the presence of an allylic tertiary hydroxy group. The compounds dissolve in cold dilute caustic soda, but not in sodium bicarbonate solution. The weak acidity is attributed to the hydroxy group and is further demonstrated by the production of O-ethers with alcohols and mineral acid. Dimethyl sulphate causes N and O-N methylation giving two products, and acetic anhydride in boiling pyridine leads to a diacetate. These results can only be explained by the cyclic structure (V). Hence the pyrrolone structure is confirmed.

In addition to the cyclic, α,β -unsaturated- γ -ketoamide described by Hill and Lutz (loc.cit.), the cyclisation of (XI; R = H or Br) to the corresponding pyrrolinones (XII; R = H or Br, R' = H) in the presence of hydrogen chloride has been described, and also the preparation of the methyl and ethyl ethers (XII; R = Br, R' = Me or Et)⁴¹.



(XI)



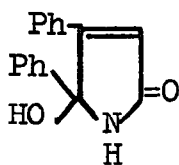
(XII)

(d) Further experiments with the pyrrolinone (V)

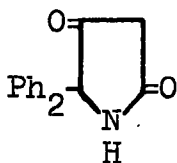
(i) Alkaline hydrolysis

a) When the pyrrolinone (V) or its hydrate is boiled

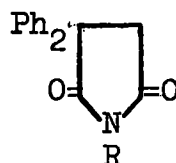
with dilute caustic soda an acid is formed, which spontaneously loses carbon dioxide on acidification of its alkaline solution. Analysis of the product leads to the formula $C_{16}H_{13}O_2N$. The compound does not react with hydroxylamine, phenylhydrazine or 2:4-dinitrophenylhydrazine, which indicates the absence of a free keto group. It is not acid to sodium bicarbonate solution, but dissolves in cold dilute sodium hydroxide to give a colourless solution, from which it precipitates unchanged on acidification. These properties are in accord with the presence of a 5-hydroxy-pyrrolinone ring (see page 30) and hence the structure (XIII) is indicated, formed by hydrolysis of the cyano group of (V) and subsequent decarboxylation.



(XIII)



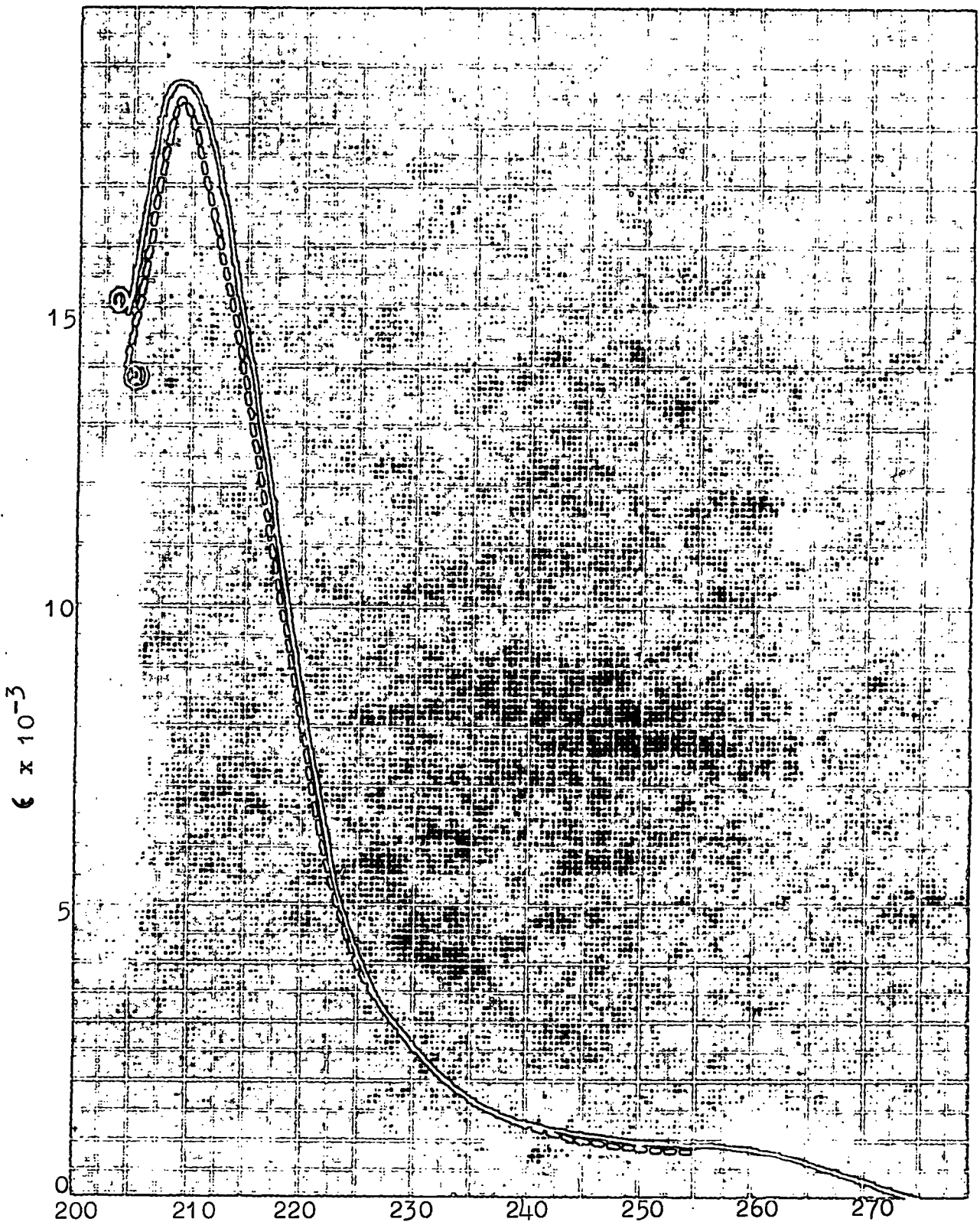
(XIV)



(XV)

The ultra-violet spectrum of the product is, however, incompatible with the pyrrolinone formulation, there being a peak at 208 μ . ($\epsilon_{\text{max.}} = 18,700$) and no maximum near 275 μ . as would be expected if the compound possessed the cinnamoyl group in (XIII), (compare Browne and Lutz, loc.cit.). This suggests that the cinnamoyl grouping has been disrupted by an intramolecular rearrangement involving

Ultra-violet Spectra (in ethanol).



α -Diphenylsuccinimide.

1....from the pyrrolinone V

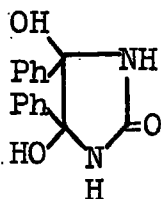
2....from α -diphenylsuccinic acid.

a phenyl group. Two possible structures for the hydrolysis product must therefore be considered. These are the 2:2-diphenylpyrrolidin-3:5-dione (XIV) and α,α -diphenylsuccinimide (XV; R = H) formulations. Of these (XIV) is eliminated by the non-ketonic nature of the hydrolysis product and also by its failure to produce a red colour with ferric chloride solution, a fact which argues against the presence of the highly labile keto-enol system in (XIV). The diphenylsuccinimide structure is therefore indicated, and is consistent with the properties listed above. Thus the solubility in alkali is attributable to the weak acidity of the N-H group.

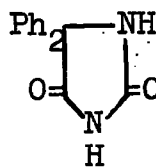
Methylation of the compound with dimethyl sulphate leads to a crystalline monomethyl derivative, m.p. 88-90°, undepressed by admixture with an authentic sample of α,α -diphenyl-N-methylsuccinimide (XV; R = Me) prepared from α,α -diphenylsuccinic and methylamine⁴⁹. The hydrolysis product is therefore α,α -diphenylsuccinimide (XV; R = H) and this is confirmed by the identity of its melting point and mixed melting point with that of an authentic specimen⁴⁹, m.p. 141-142°C., which also has the same ultra-violet spectrum.

b) Mechanism

The rearrangement of (XVI) to diphenylhydantoin (XVII) in the presence of caustic soda has been reported to involve a pinacol-pinacolone rearrangement⁵⁰.

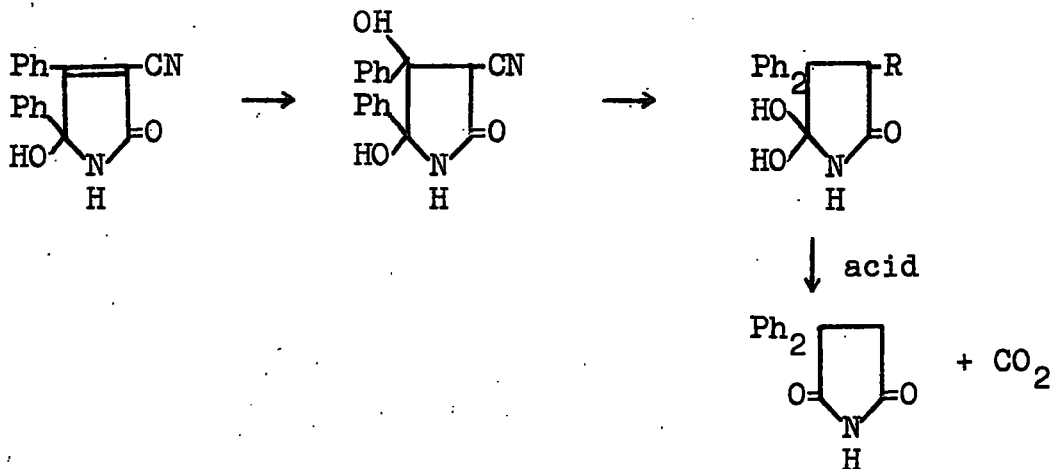


(XVI)

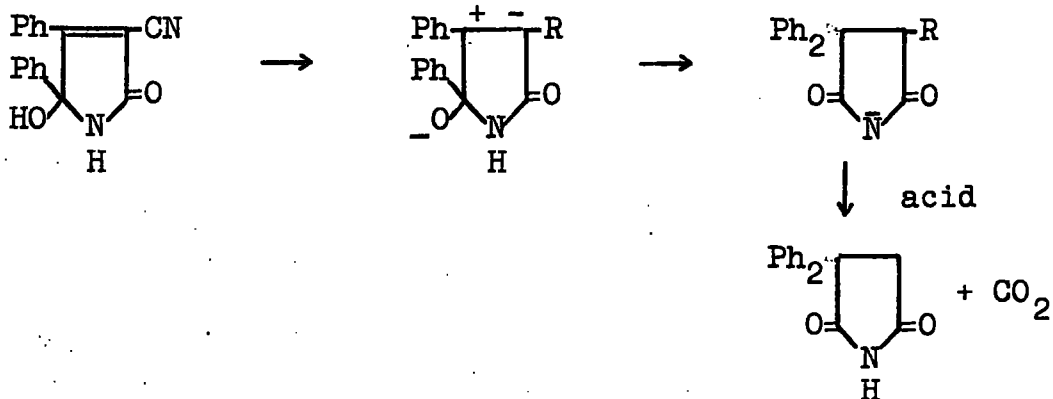


(XVII)

In the rearrangement of (V) therefore hydration of the α,β -double bond may lead to the following mechanism:-



However, the pinacol-pinacolone rearrangement is usually induced by strong acids. A preferable mechanism, analogous to the benzil-benzilic acid rearrangement (compare Ingold⁵¹) which is also conducted under alkaline conditions, is the following:-



The cyano group is hydrolysed at some stage during the reaction, the exact point being uncertain as indicated by the symbol R in the above structures.

(ii) Attempts at dehydration

It was hoped at this stage that the removal of the elements of water from the pyrrolinone (V) to give the pyrrolenone (II; R = Ph) would be readily accomplished. Such has not proved to be the case. The following experiments have not yielded the desired compound.

a) Prolonged heating at the melting point in a stream of dry nitrogen causes decomposition of both the pyrrolinone and its hydrate. Examination of the resulting black tars has not led to identifiable products.

b) In the presence of an equivalent of phosphorus pentoxide in benzene (or chloroform) the pyrrolinone and its hydrate yield only the anhydrous pyrrolinone together with a small amount of a red gum.

c) Brief heating with phosphorus oxychloride leads to amorphous products which cannot be recrystallised. Analysis of the crude dried solids does not lead to formulæ from

which probable structures can be deduced.

d) Acetic anhydride in the cold is without effect and under more vigorous conditions, blue solutions rapidly form, which on prolonged heating deposit black tars. Evaporation of such solutions before tar formation leads to black solids which cannot be recrystallised. Attempts to resolve the products on alumina columns, eluting with a variety of solvents, is unsuccessful in effecting any purification.

e) Cold concentrated sulphuric acid is without effect. Under more vigorous conditions decomposition occurs.

f) Polyphosphoric acid has been widely used as a cyclising agent^{52,53}. The reaction of the pyrrolinone (V) or its hydrate with polyphosphoric acids of various strengths (see Bell⁵⁴) does not lead to the desired product. Yellow amorphous solids, which recrystallise (with difficulty) from only acetic^{acid} (80%), result from these reactions. As none of the products melt no ready criterion of purity is available and analyses of several samples have not given consistent figures. The products may in fact be polymers.

The pyrrolenone ring thus appears to be difficult to synthesise from (V), and may even be too unstable to exist at all.

2. The reaction of cyanoacetamide with aliphatic 1:2-diketones and with the pyrrolinone (V) described in (1).

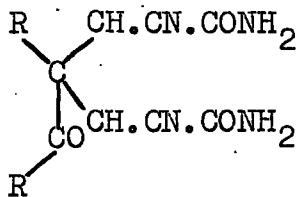
A. Diacetyl

When diacetyl and cyanoacetamide react under the influence of piperidine a colourless, crystalline, high-melting solid results. It is appreciably soluble only in water and hot ethanol, being almost insoluble in other media. Reaction conditions for good yields are remarkably critical. Although water is a suitable solvent in which to conduct the reaction, better yields are obtained by the use of ethanol, probably as a result of the compound's much lower solubility in this medium. In order to avoid the production of dark by-products of uncertain constitution, the temperature must be maintained between 50 and 60°C. Observance of these conditions together with gradual addition of the diacetyl to a well-stirred solution of the other reactants leads to an excellent yield of the product described, in a high state of purity.

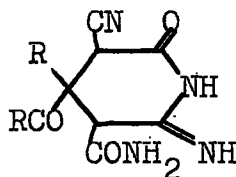
(a) Structure of the product

Analysis for C, H, and N leads to the formula $C_{10}H_{12}O_3N_4$ indicating that one molecule of diacetyl and two molecules of cyanoacetamide react with elimination of one molecule of water. Five possible structures (XVIII; R

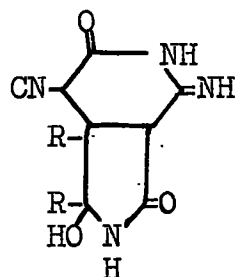
= Me) - (XXII; R = Me) must therefore be considered.



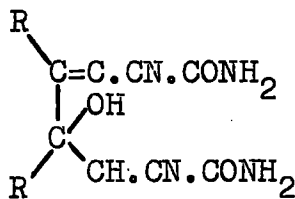
(XVIII)



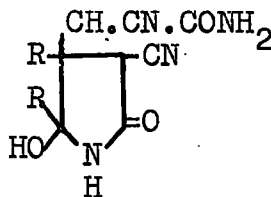
(XIX)



(XX)



(XXI)



(XXII)

The following experiments provide a basis for choice between these alternatives.

(i) The compound does not react with hydroxylamine, semicarbazide, phenylhydrazine or 2:4-dinitrophenylhydrazine. It therefore either contains no free keto group or steric hindrance by the adjacent groups screens this centre and thereby prevents reaction. The first of these alternatives eliminates the simple structure (XVIII; R = Me) and the monocyclic structure (XIX; R = Me) if further evidence can be produced.

(ii) Dilute potassium permanganate solution is not decolourised by addition to a solution of the compound in water. This

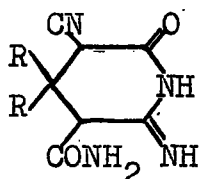
indicates the absence of ethylenic linkages in the molecule. The ultra-violet spectrum does not exhibit a peak near 210 μ . showing that the compound has no α, β -unsaturation. (iii) The compound does not react with acetyl, benzoyl, or *p*.toluene sulphonyl chlorides nor with acetic anhydride. This points to the absence of a hydroxy group in the β -position with respect to the amido and cyano groups, for a compound possessing this group would be expected either to form esters or to easily dehydrate during the attempts to prepare them.

Points (ii) and (iii) thus dispose of (XXI; R = Me) as a possible structure for the high melting compound.

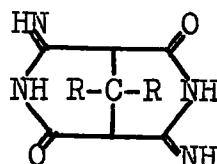
(iv) The compound is recovered unchanged after prolonged refluxing in an aqueous solution. This indicates the absence of an imino-group in the molecule, and hence that (XIX; R = Me) and (XX; R = Me) are not correct. Such structures would be expected to hydrolyse under the action of boiling water to yield the corresponding imides (cf. Thorpe et al., loc.cit.).

(v) Thorpe and his co-workers^{20,21,22,23} have shown that the simple imino-imides (XXIII; R = alkyl) and (XXIV; R = alkyl) yield crystalline mono- and di-platini-chlorides respectively when reacted with cold platinic chloride solution. No such derivative is precipitated employing a

solution of the above compound in the same way. The inference from this is that it does not have an imino-imide ring, and therefore that the configurations (XIX; R = Me) and (XX; R = Me) do not represent its structure.



(XXIII)



(XXIV)

The evidence so far presented argues against the four possibilities (XVIII-XXI; R = Me) and consequently the pyrrolidone formulation (XXII; R = Me) is preferred.

Further work shows that this is in fact correct.

(b) Evidence supporting the pyrrolidone structure

This evidence is conveniently divided into (i) evidence for the presence of a pyrrolidone ring - the effect of cold concentrated sulphuric acid, (ii) evidence against the possibility of formation of an imino-imide ring - the effect of sodium ethoxide.

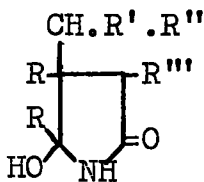
(i) Evidence for the presence of a pyrrolidone ring - the effect of cold concentrated sulphuric acid

The compound dissolves in cold 90% sulphuric acid. This solution, on dilution after 36 hours, gradually deposits colourless crystals of a high-melting acid. Analysis leads to the formula $C_{10}H_{13}O_5N_3$ and titration with standard

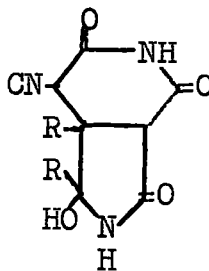
sodium hydroxide solution gives an equivalent weight of 256. ($C_{10}H_{13}O_5N_3$ requires 255). The product is therefore a mono-basic acid and contains one carboxyl group.

This acid is unreactive towards hydroxylamine, semicarbazide and 2:4-dinitrophenylhydrazine. This indicates the probable absence of a free keto group, and would be explained by the interaction of keto and amido groups to form a pyrrolidone ring.

The simplest explanation of these facts is that one amido group hydrolyses to a carboxyl group and that one cyano group hydrolyses to an amido group. This is consistent with the presence of only one amide group in the molecule and hence with the pyrrolidone structure. In this molecule it might be supposed that the two differently sited cyano groups would have different rates of hydrolysis, thus accounting for the reaction of only one of them under the conditions described.



(XXV)



(XXVI)

On the basis of this conception of the course of the reaction the acid has therefore the structure (XXV; R =

Me, R' = COOH; either R'' = CONH₂, R''' = CN; or R'' = CN, R''' = CONH₂).

The production of this acid therefore shows that the compound contains one protected amido-group and that on hydrolysis ketonic properties are not produced. It also shows that the two cyano groups are differently situated with respect to adjacent groups and thus argues in favour of the presence of a pyrrolidone ring in the molecule. This reaction does not preclude the bicyclic structure (XX; R = Me) as an intermediate in the hydrolysis. Conversion of this to the imide (XXVI; R = Me) would then be expected (cf. Thorpe et al., loc.cit.), and addition of water to the imide grouping would lead to two possible acids C₁₀H₁₃O₅N₃, of which (XXV; R = Me, R' = CN, R'' = CONH₂, R''' = COOH) is a third possibility for the high melting acid.

The latter possibility is considered to be unlikely. Thorpe and his associates have shown that the imino-imides (XXIII and XXIV; R = alkyl) are converted by cold concentrated sulphuric acid to the corresponding imides. These are stable under the reaction conditions employed, and it seems unlikely that (XXVI; R = Me) would be hydrolysed to the mono acid. In the next section it will be shown that the route is in fact not possible.

(ii) Evidence against the possibility of formation of an imino-imide ring - the effect of sodium ethoxide

The presence of the pyrrolidone ring is established by the above experiments and in addition the possible presence of a second six-membered imino-imide ring is discounted. The absolute configuration of the pyrrolidone has not yet been fully ascertained, however, since two formulations are possible. The cyano and cyanoacetamido substituents can have two possible arrangements with respect to each other, above and below the pyrrolidone ring.

If they are cis then interaction between them would lead to the bicyclic imino-imide (XX; R = Me). The evidence for this is provided by the work of Thorpe et al. (loc.cit.) who have shown that the condensation of aliphatic ketones with cyanoacetamide, under basic conditions, gives imino-imides (XXIII; R = alkyl). In these the cyano and amido groups are cis with respect to each other, and under the influence of cold sodium ethoxide ring closure occurs giving the bicyclic imino-imides (XXIV; R = alkyl), which separate as sodio derivatives. Solution of the salts in water and acidification with acetic acid leads to the sodium free compounds.

If in the pyrrolidones the configuration is trans only the monocyclic structure (XXII; R = Me) is possible.

The pyrrolidone does not react with cold ethanolic sodium ethoxide. Unchanged starting material is recovered even after several hours shaking. This observation provides strong evidence against a cis formulation. The compound $C_{10}H_{12}O_3N_4$ is therefore the pyrrolidone (XXII; R = Me) in which the configuration of the cyano and cyanoacetamido substituents is trans.

(c) Recapitulation

The reaction of diacetyl with cyanoacetamide under the influence of piperidine leads to a product $C_{10}H_{12}O_3N_4$. Five possible structures can be envisaged for this. These are the formulations (XIV-XVIII; R = Me).

The compound does not react with hydroxylamine, semicarbazide, phenylhydrazine or 2:4-dinitrophenylhydrazine. This fact indicates that it contains no free keto group. It does not yield derivatives with acyl or p.toluenesulphonyl chlorides nor with acetic anhydride. This indicates that unhindered hydroxy groups are not present. Potassium permanganate solution is not decolourised by the compound, a fact which indicates the absence of ethylenic linkages. α,β -Unsaturation is shown to be absent by the ultra-violet absorption spectrum which exhibits no maximum near 210 μ . Boiling water is without effect, which argues against the presence of an imino-imide ring. This is also supported by

the non-formation of a platinichloride.

The above facts eliminate the four alternatives (XVIII-XXI; R = Me) and thus only the pyrrolidone structure (XXII; R = Me) is left for consideration.

This structure is supported by hydrolytic studies with (i) cold concentrated sulphuric acid; and (ii) cold sodium ethoxide. With the former reagent a non-ketonic acid $C_{10}H_{13}O_5N_3$ results, most plausibly by hydrolysis of one cyano and one amido group to an amido and carboxyl group respectively. Thus, the compound contains only one free amido group. The other is hence protected by interaction with the keto group and so the compound contains the pyrrolidone ring. The pyrrolidone does not react with cold ethanolic sodium ethoxide.

It has been shown that these results are best explained by the pyrrolidone structure in which the cyano and cyanoacetamido substituents are trans with respect to one another. Consequently the bicyclic structure (XX; R = Me) cannot be formed, and hence cannot participate as an intermediate in any of the reactions detailed above.

The pyrrolidone structure with the trans configuration described is therefore proved, and fully explains the observed properties of the compound $C_{10}H_{12}O_3N_4$, obtained from the reaction of diacetyl and cyanoacetamide.

(d) Attempts to obtain other reaction products

(i) The effects of bases other than piperidine in the reaction have been studied. No other reaction products to that described above have been isolated.

a) Sodium ethoxide - This base in the cold leads to rapid formation of dark solutions, probably due to polymerisation of the diacetyl. These solutions after evaporation and titration with dilute hydrochloric acid, yield black aqueous solutions which gradually deposit a small amount of the acid $C_{10}H_{13}O_5N_3$ (see page 43).

b) Sodium hydroxide - leads to the rapid formation of dark solutions from which a small amount of the pyrrolidone separates over several days. Cyanoacetamide can be recovered from the mother liquors but no diacetyl can be ether extracted.

c) Pyridine and secondary or tertiary amines (diethylamine and triethylamine) - are ineffective in promoting reaction. The cyanoacetamide can be recovered after several days. The diketone, however, is destroyed since it cannot be recovered.

d) Sodium acetate - causes only slow destruction of the diketone, but the cyanoacetamide can be quantitatively recovered.

(ii) Sulphuric acid has also been employed as a possible catalyst. It is ineffective in promoting reaction. The diacetyl can be recovered even after several days.

(iii) Refluxing the reactants in aqueous or ethanolic solution without the use of condensing agents leads to no reaction, nor are products obtained by adding diacetyl to fused cyanoacetamide.

B. Similar products obtained from other 1:2-diketones and from the pyrrolinone (V)

Dipropionyl and dibutyryl react with 2 molecules of cyanoacetamide to yield products $C_{12}H_{16}O_3N_4$ and $C_{14}H_{20}O_3N_4$ respectively. Considerable alteration of the reaction conditions are necessary with the latter diketone, from which the product is obtained in only low yield (10%). The piperidine is added dropwise, in the form of a 10% aqueous solution, to a cold, stirred aqueous solution of the other reactants. The product separates after a few minutes as oil which rapidly solidifies and is filtered off after several days, during which time further small quantities of the products are formed. Both of the above compounds are high melting solids which are appreciably soluble only in hot ethylene glycol, from which they are in fact recrystallised.

Under reflux in ethanol the pyrrolinone (V) (or its hydrate) adds a further molecule of cyanoacetamide to give a high melting solid $C_{20}H_{16}O_3N_4$. This compound is almost insoluble in normal solvents even in the hot.

The formulæ of these products suggest that they

are in fact similar to the product from diacetyl and cyanoacetamide. They would therefore be the pyrrolidones (XVIII; R = Et; Pr and Ph). Comparison of their properties with those of the dimethyl pyrrolidone leads to the conclusion that they in fact do have similar structures. The proof of this is conveniently divided into (a) chemical evidence (b) spectroscopic evidence.

(a) Chemical evidence

(i) The compounds do not react with 2:4-dinitrophenylhydrazine. Because of their great insolubilities in normal solvents attempts to prepare such derivatives have to be conducted in 90% sulphuric acid (cf. Brady⁵⁵). The compounds do not therefore appear to contain any free keto groups.

(ii) They dissolve in cold 90% sulphuric acid (gentle warming is necessary in the case of the diphenyl analogue) and the solutions obtained on dilution after 48 hours, slowly deposit colourless high melting solids.

The diethyl analogue yields a mono-basic acid $C_{12}H_{17}O_5N_3$, probably the pyrrolidone (XXV; R = Et, R' = COOH; either R'' = CONH₂, R''' = CN; or R'' = CN, R''' = CONH₂). The dipropyl analogue gives a non-acidic product analysing as $C_{14}H_{23}O_6N_3$. No satisfactory structure can be deduced for this product which may be a mixture. The diphenyl compound yields by a similar reaction a non-acidic product $C_{18}H_{17}O_3N_3$,

a formula which indicates that the expected acid has lost carbon dioxide. The product is therefore the pyrrolidone (XXV; R = Ph; R' = H; either R'' = CONH₂, R''' = CN; or R'' = CN; R''' = CONH₂). This product is usually contaminated with unreacted material from which it can be extracted with hot ethylene glycol. The product from the dipropyl analogue may possibly be a similar mixture but no separation is possible in this case. The chemical evidence thus supports the pyrrolidone formulation for the compounds.

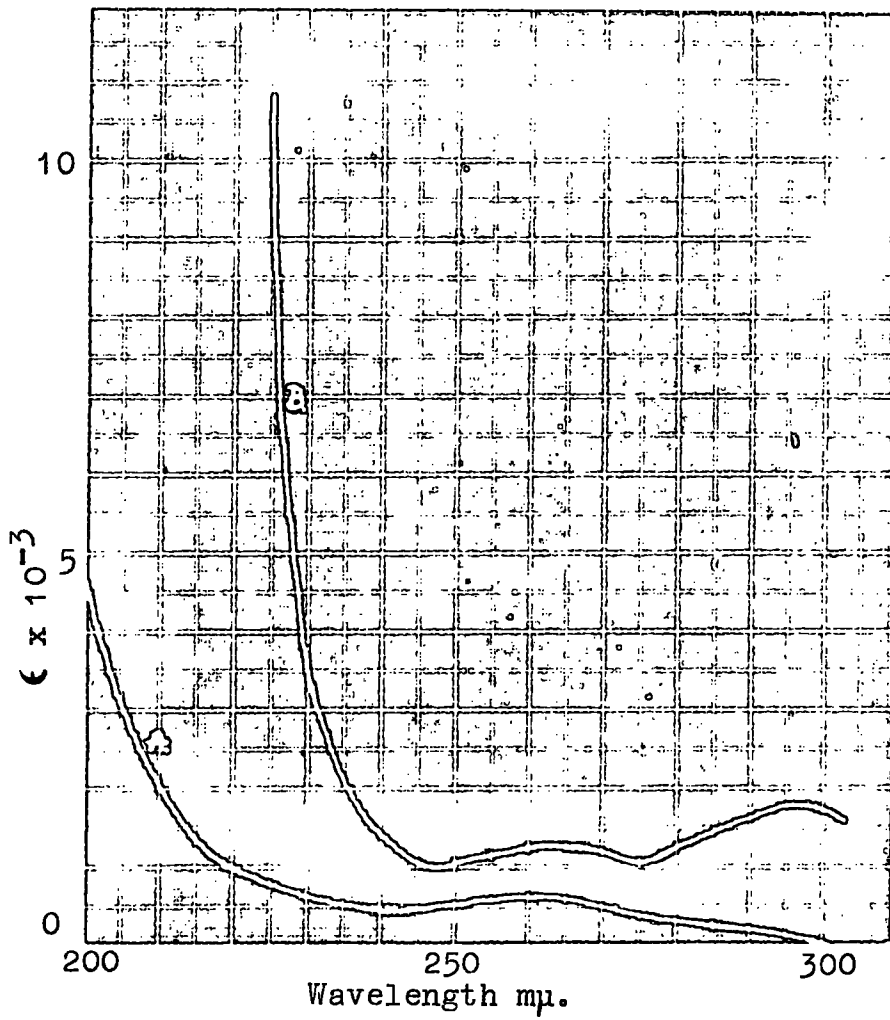
(b) Spectroscopic evidence

(i) Ultra-violet spectra

Only the diphenyl analogue has been studied in the ultra-violet region. It was hoped to confirm for this compound, the absence of a free benzoyl group, which would be expected to absorb near 245 m μ . (cf. Browne and Lutz, loc.cit.), and also to show that it contains no α -cyanocinnamoyl grouping with a characteristic absorption band near 295 m μ . The aliphatic analogues would not be expected to absorb in this region.

No absorption maxima are in fact observed near 245 m μ . and 295 m μ . The diphenyl compound does not therefore contain a free benzoyl group nor the α -cyanocinnamoyl group. The presence of the pyrrolidone ring is therefore confirmed for this compound, and by analogy it may reasonably be assumed that the aliphatic compounds are also similar.

Ultra-violet Spectra.



A.....(XXII;R=Me),in water. . .

B.....(XXII;R=Ph),in ethanol.

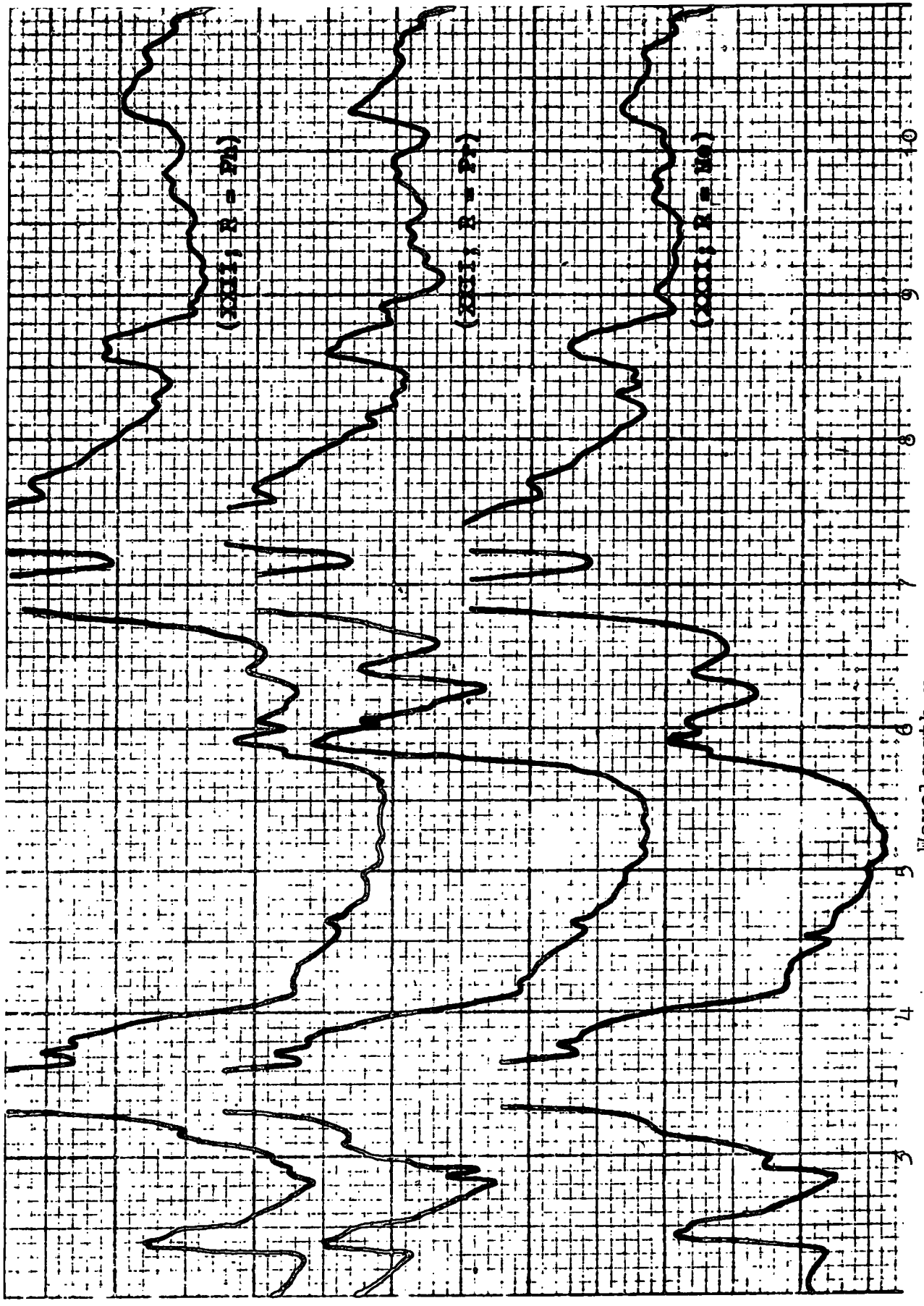
(ii) Infra-red spectra

The infra-red spectra of the dimethyl, dipropyl, and diphenyl compounds, in nujol mull, have been compared. Their great similarity confirms that all three must have similar structures, but no unambiguous evidence for the pyrrolidone formulations can be obtained from them. The difficulties arising at this point are as follows:-

- a) The insolubilities of the compounds in suitable solvents makes it necessary to use the solids for measurements in the infra-red. The location of bands is less certain under these conditions.
- b) Chromophores such as the amido, imino, and keto groups exhibit their most characteristic absorptions in the 5-6 μ . region and as these groups are in fact the very ones needing consideration, assignments are rendered difficult.
- c) The combination of these two factors makes considerable overlapping very probable, thus creating further uncertainties.

Despite these difficulties the following assignments are tentatively made on the basis of the pyrrolidone structures for which other evidence has been presented.

Infra-red Spectra (in nujol mull).



Frequency	Assignment
5.90 μ .	Free amide and γ -lactam carbonyls
6.05 μ .	The amide (II) band (N-H stretching) due to the free amide group.

The rather weak bands near 2.85 are tentatively assigned to the tertiary hydroxy group, but may well be N-H stretching frequencies. A further band at 8.7 μ . is also consistent with the presence of the hydroxy group in these compounds. It is significant that the 5-hydroxypyrrolinone (V) shows such a maximum whereas the derived 5-methoxypyrrolinone (X; R = H, R' = Me) does not. Bellamy and Weissberger (loc.cit.) both discuss the infra-red absorptions of organic compounds in some detail, and these sources provide the basis on which the assignments are made.

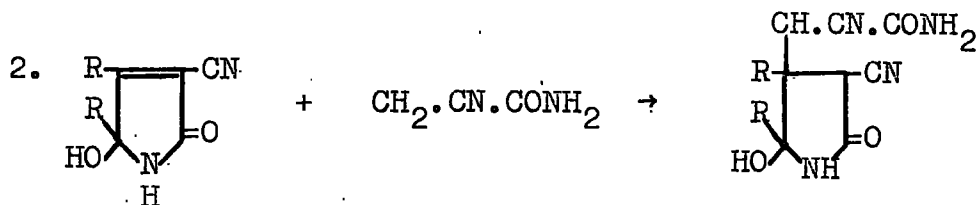
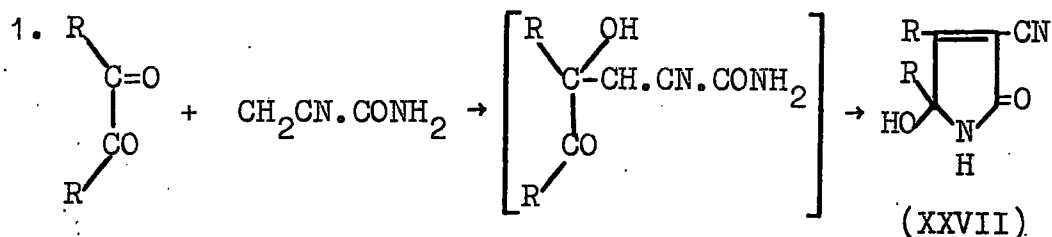
(c) Recapitulation

The condensation of 1:2-diketones with two molecules of cyanoacetamide in the presence of piperidine is accompanied by loss of a molecule of water and production of the pyrrolidones (XXII; R = Me, Et, Pr, and Ph) in which the cyano and cyanoacetamide substituents are trans with respect to each other, above and below the pyrrolidone

ring. In the preceding pages these structures have been supported by chemical and spectroscopic evidence which has eliminated other alternative structures.

(d) Probable Mechanism

The reaction of benzil with one molecule of cyanoacetamide to yield the pyrrolinone (V), which can be further reacted with a second molecule of cyanoacetamide to give the pyrrolidone (XXII; R = Ph), points to the mechanism, since it is probable that two similar steps occur with the aliphatic diketones. The proposed mechanism is:-



(i) The first stage is a Knoevenagel reaction between one keto group of the diketones and the active methylene group of cyanoacetamide to give α,β -unsaturated- γ -ketoamides which probably immediately cyclise to the 3-cyano-4:5-dialkyl (or phenyl)-5-hydroxy-2-pyrrolinones (XXVII). These are probably rapid reactions.

(ii) The second stage is an example of the Knoevenagel addition of the cyanoacetamide to the α,β -double bond of (XXVII) to give the pyrrolidones. In the aliphatic series this appears also to be a rapid stage, but with benzil a much slower addition occurs, and then only at elevated temperatures. Steric hindrance probably retards this reaction.

3. The glutaro-dilactones and attempts to synthesise them

(a) Preparation

When the pyrrolidones described above, or the acids (XXV) derived from them by partial hydrolysis (pages 43 and 51), are boiled with 8 N. sulphuric acid (or 80% sulphuric acid in the case of diphenyl compounds) they are converted to non-nitrogenous products, which analyse as $C_8H_{10}O_4$, $C_{10}H_{14}O_4$, $C_{12}H_{18}O_4$ and $C_{18}H_{14}O_4$. These were obtained in the following yields from the corresponding pyrrolidone.

Pyrrolidone XVII; R =	Product	Yield %
Me	$C_8H_{10}O_4$	95
Et	$C_{10}H_{14}O_4$	95
Pr	$C_{12}H_{18}O_4$	90
Ph	$C_{18}H_{14}O_4$	10

(b) Properties

(i) Acidity

The products are not acid towards sodium bicarbonate solution nor are they soluble in cold dilute sodium hydroxide. Their solutions in boiling water, however, may be titrated with standard alkali, and hence their equivalent weights can be determined. These correspond to half the molecular weights calculated on the above formulæ. Two potential carboxylic acid groups are thus indicated for the compounds, a fact which suggests the presence of either two lactone rings, or less likely, two ester groups or an anhydride group.

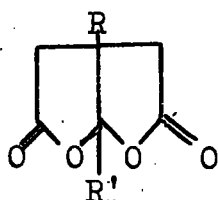
Acidification of the solutions obtained by boiling with dilute caustic soda regenerates the original neutral compounds, a fact which points to the first of these alternatives

(ii) The action of 2:4-dinitrophenylhydrazine

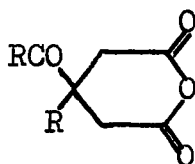
The aliphatic analogues react with this reagent yielding pale yellow products. These analyse as mono 2:4-dinitrophenylhydrazones in the cases of the dimethyl and dipropyl analogues. The diethyl product has not been obtained in a pure state despite the use of chromatographic techniques, but appears to be similar in nature. The diphenyl analogue does not react with this reagent, nor with hydroxylamine, semicarbazide or phenylhydrazine. This may be due to the influence of steric hindrance.

(c) Structure

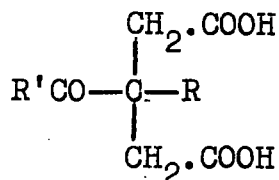
Consideration of the formulæ and properties of the products leads to two alternatives for their structures. These are the dilactone (XXVIII; R = R' = Me, Et, Pr, and Ph) and the keto anhydride (XXIX; R = Me, Et, Pr, and Ph) formulations.



(XXVIII)

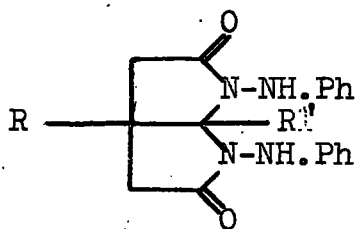


(XXIX)

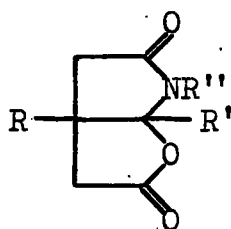


(XXX)

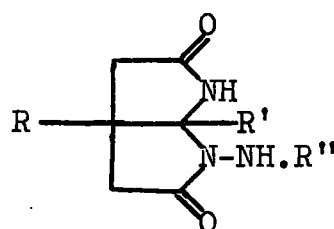
The formation of these compounds in acid, and their regeneration by acids after alkaline hydrolysis points to the dilactone structures, but it would be expected that they would yield di-derivatives with 2:4-dinitrophenylhydrazine, unless steric hindrance prevents this. Emery⁵⁶ has shown that β -acetylglutaric acid (XXX; R = H, R' = Me) gives the dilactone (XXVIII; R = H, R' = Me) in the presence of hydrochloric acid and that this yields a di-derivative (XXXI; R = H, R' = Me) when reacted with phenylhydrazine in acetic acid.



(XXXI)



(XXXII)



(XXXIII)

In order to obtain evidence for the dilactone structure, therefore, the dimethyl compound has been further investigated and the results will now be presented.

(d) Further reactions of the dimethyl analogue

(i) Reaction with phenylhydrazine in acetic acid under reflux leads to a crystalline solid $C_{20}H_{22}O_2N_4$, a formula showing that two molecules of phenylhydrazine and one of the compound have reacted with elimination of water. This di-derivative is analogous to Emery's product from (XXVIII; R = H, R' = Me) and phenylhydrazine, and probably has a similar structure (XXXI; R = R' = Me).

(ii) Reaction with ethanolic ammonia leads to a crystalline nitrogenous product $C_8H_{11}O_3N$, showing that one molecule of ammonia has reacted with one of the compound with elimination of a molecule of water. Reaction with 2:4-dinitrophenylhydrazine leads to a mono-derivative identical with the product obtained by reacting the mono-2:4-dinitrophenylhydrazine derivative (page 57) with ethanolic ammonia. The products are probably the lactam-lactone (XXXII; R = R' = Me, R'' = H) and (XXXIII; R = R' = Me, R'' = 2:4-(NO₂)₂C₆H₃). Similar products (XXXII; R = R'' = H, R' = Me) and (XXXIII; R = H, R' = Me, R'' = Ph) have been prepared from the dilactone (XXVIII; R = H, R' = Me). (Emery, loc.cit.).

(iii) The dimethyl compound is not oxidised by alkaline hypobromite or hypochlorite nor does reaction with iodine and caustic soda yield any iodoform. The absence of a free acetyl group is therefore indicated, providing further argument against the keto-anhydride formulation.

The dilactone structure is hence confirmed for the dimethyl compound, and by analogy the diethyl, dipropyl and diphenyl analogues have similar structures.

Attempts to react the diphenyl dilactone with ethanolic ammonia are unsuccessful, probably due to steric hindrance by the bulky phenyl substituents.

(e) Recapitulation

Hydrolysis of the pyrrolidones (XXII; R = Me, Et, Pr and Ph) with strong sulphuric acid under reflux, leads to neutral crystalline products which by analysis, and by their titration with standard alkali, are shown to be either the dilactones (XXVIII; R = R' = Me, Et, Pr, and Ph) or the keto-anhydrides (XXIX; R = Me, Et, Pr and Ph). Acidification of the solutions obtained by boiling with alkali causes regeneration of the neutral compounds, a fact which favours the dilactone formulation. On the other hand, the aliphatic compounds yield only mono-derivatives with 2:4-dinitrophenylhydrazine. This is more in accord

with the keto-anhydride structure.

Further reactions with the dimethyl analogue, however, show conclusively that it has the dilactone structure. With phenyl hydrazine in boiling acetic acid it yields a bis-phenylhydrazone, a derivative shown by Emery (loc.cit.) to be characteristic of a similar dilactone (XXVIII; R = H, R' = Me). Two other characteristic derivatives are obtained by reacting the dilactone with ethanolic ammonia to give a lactam-lactone (XXXII; R = R' = Me, R'' = H) which gives a mono-derivative with 2:4-dinitro-phenylhydrazine.

The diphenyl analogue is inert to these reagents, but its physical properties suggest that it has the same structure.

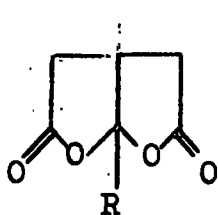
Hence, the dilactone formulation is proved for the dimethyl analogue, and by analogy for the diethyl, dipropyl and diphenyl analogues.

(f) Attempts at synthesis

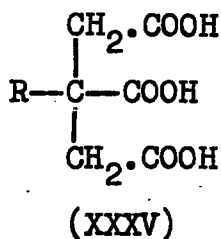
The dimethyl dilactone was chosen for these attempts as in general starting materials of known structure are more readily available.

(i) Fittig and Roth⁵⁷ have prepared several similar dilactones (XXXIV; R = alkyl or aryl) by the reaction of the sodium salt of tricarballic acid (XXXV; R = H) with

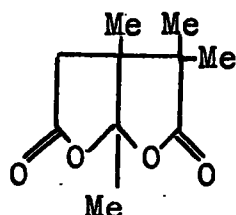
acid anhydrides at 130-140°C. for several hours. Fittig and Salomon⁵⁸ have also prepared the dilactone (XXXVI) in 3% yield by a similar route from α,α,β -trimethyltricarballic (camphoronic) acid and acetic anhydride.



(XXXIV)



(XXXV)



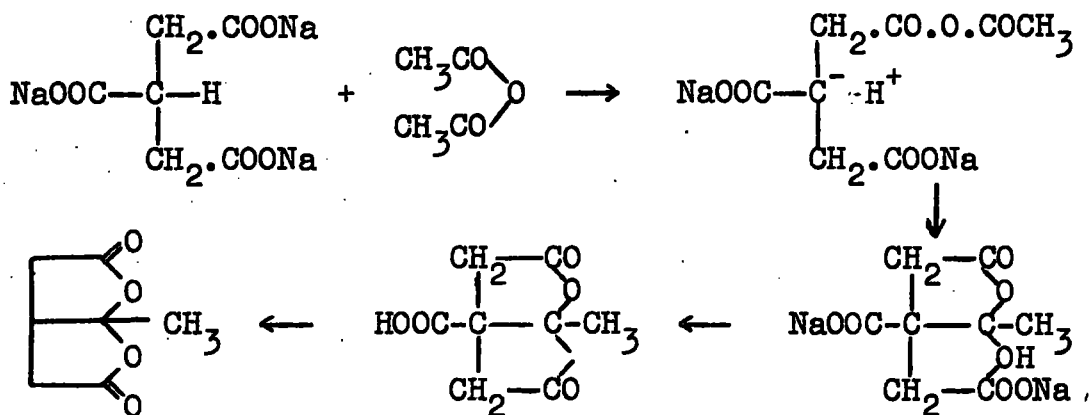
(XXXVI)

β -Methyl tricarballic acid (XXXV; R = Me) in the form of its sodium salt, does not react with acetic anhydride even under reflux for several days. The potassium and ammonium salts are similarly unreactive and benzoyl peroxide, sodium acetate and small amounts of acetyl chloride are ineffective in promoting the reaction. The unchanged acid is quantitatively recovered from these reactions.

The use of the free acid in refluxing acetic anhydride (cf. McEwen and Mehta⁵⁹) does not lead to reaction, nor are products obtained by the use of acetyl chloride.

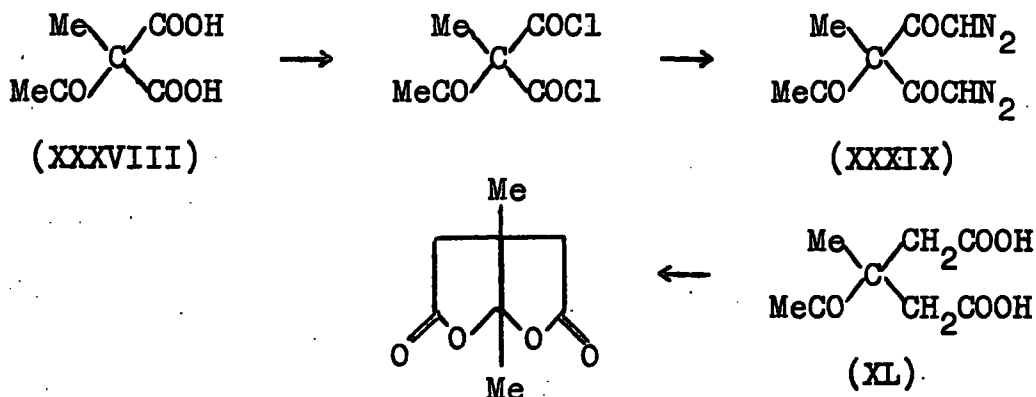
A possible explanation of the above unreactivity lies in the fact that the β -position is fully substituted. If it is postulated that dilactone formation requires an easily polarisable C-H bond on this atom, the failure to obtain the required dilactone from β -methyl tricarballic

acid is explained. The following mechanism is therefore suggested:-

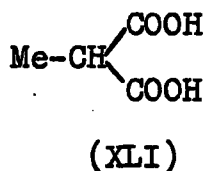


Apart from the anomaly of the camphoronic acid reaction (loc.cit.) there is no data in the literature contradicting this mechanism. The isolated case of camphoronic acid may, in view of the low yield, be due to this acid containing an impurity. It is suggested that this may be $\alpha:\alpha:\gamma$ -trimethyltricarballic acid.

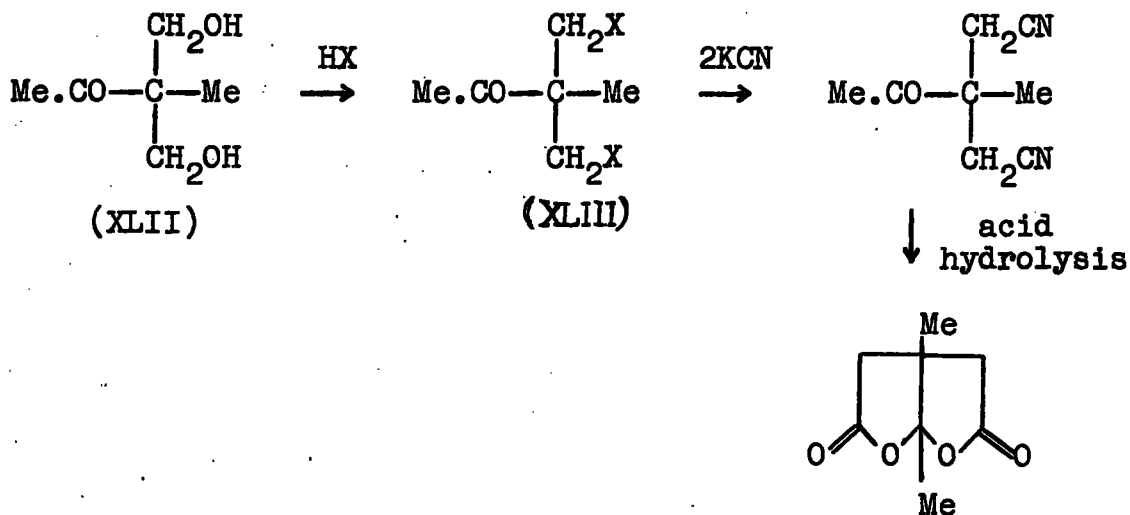
(ii) A second possible route to the dimethyl dilactone is from acetyl-methyl-malonic acid (XXXVIII). This with thionyl chloride or phosphorus pentachloride might yield the dichloride, which with diazomethane would give the corresponding diazo-ketone (XXXIX). Reaction of this with moist silver oxide would then lead to the ketoglutaric acid (XL) and thence to the dimethyl dilactone.



The diethyl ester of acetyl-methyl-malonic acid does not, however, yield the required acid on hydrolysis. With sodium hydroxide a salt is obtained, which on acidification yields methyl malonic acid (XLI).



(iii) It has been reported⁶⁰ that the reaction of methyl ethyl ketone and formaldehyde under the influence of dilute caustic soda, leads to mixtures from which 3:3-bis-hydroxy-methyl-2-butanone (XLII) can be isolated. This compound has been prepared in low yield. It was proposed to employ the following route to the required diketone:- (X = Br, Cl, or I).



With concentrated hydrochloric acid, however, a mixture is obtained which does not fractionate, and which, from analytical results on a sample of a distilled specimen, appears to have only about half the required amount of chlorine. Cold hydrogen bromide, either in the gaseous form or in concentrated aqueous solution, leads to a colourless liquid, boiling point $108^{\circ}/5$ mm., which contains only half the required amount of bromine and has not been further investigated, (compare Déscombe⁶¹). At elevated temperature black tars are formed, and similarly tars result when hydrogen iodide is used.

An alternative route to the iodide (XLIII; X = I) from the bis-*p*-toluenesulphonate (XLVII; X = *p*.MeC₆H₄SO₃) by reaction with sodium iodide (compare Baer and Fischer⁶²) has proved unsuccessful. *p*-Toluene sulphonyl chloride reacts

with the dihydroxyketone (XLII) in the presence of piperidine or caustic soda, to yield an oil which does not give the required iodide with the reagents described.

The dilactone structure of the dimethyl homologue has not therefore been confirmed by an independent synthesis, but the chemical evidence presented in previous pages nevertheless points conclusively to such formulations for the hydrolysis products.

-----ooOoo-----

Summary

One molecule of benzil and one molecule of cyanoacetamide react in the presence of piperidine to yield a non-ketonic hydroxypyrrolinone (V), in the form of a hydrate from which the anhydrous (V) is obtained by recrystallisation from pyridine or by boiling in benzene. The same products result from reaction of ethyl-3-benzoyl-2-cyanocinnamate (III) with ethanolic ammonia.

The ultra-violet spectra of the hydrate and pyrrolinone are consistent with the hydroxypyrrolinone structures, there being cinnamoyl absorption at 290 m μ ., but no benzoyl band near 245 m μ .. In contrast (III) has two peaks at 247 and 285 m μ ..

The infra-red spectra are also in accord with the cyclic structures, (V); and its hydrate each having a single peak at 5.85 μ .. whereas (III) has an additional benzoyl peak at 6.05 μ ..

The presence of the allylic hydroxyl group accounts for the weak acidity. Both hydrate and pyrrolinone dissolve in dilute caustic soda and on acidification of the solution so obtained the hydrate precipitates. With methanol (or ethanol) containing hydrogen chloride O-alkyl derivatives (X; R = H, R' = Me or Et) are obtained and dimethyl sulphate gives an N-methyl and an O:N-dimethyl derivative. Acetic

anhydride in hot pyridine yields a diacetate.

When the pyrrolinone (or its hydrate) is boiled with dilute caustic soda a rearrangement involving the 2-phenyl substituent occurs and the product is α,α -diphenylsuccinimide. This is confirmed by the identity of the melting point and mixed melting point with an authentic sample, which has the same ultra-violet spectrum, and by methylation with dimethyl sulphate to give α,α -diphenyl-N-methyl succinimide, identical with a genuine sample.

Diacetyl, dipropionyl, and dibutyryl react with two molecules of cyanoacetamide with loss of a molecule of water to give the non-ketonic hydroxypyrrolidones (XXII; R = Me, Et, or Pr) and a diphenyl analogue results by further reaction of (V) with a molecule of cyanoacetamide.

The pyrrolidone formulations are supported by the ultra-violet spectra of the dimethyl and diphenyl compounds, which have no absorption maxima, due to α,β -unsaturation or a benzoyl group.

Since on boiling with water no ammonia is evolved and since no reaction occurs with cold ethanolic sodium ethoxide, the cyano and cyanoacetamido groups are trans, for if cis interaction between them would be expected to yield easily hydrolysed imino-imides (XX; R = Me, Et, Pr, and Ph). Hydrolysis with cold 90% sulphuric acid gives mono-basic acids,

probably (XXV; R = Me or Et, R' = COOH, either R'' = CONH₂, R''' = CN, or R'' = CN, R''' = CONH₂). The diphenyl acid loses carbon dioxide to give a non-acidic product.

When either the above acids or the pyrrolidones are refluxed with 8 N. sulphuric acid (or 80% in the case of the diphenyl analogues) they are converted to the dilactones (XXVIII; R = R' = Me, Et, Pr, and Ph). The aliphatic compounds yield mono-derivatives with 2:4-dinitrophenylhydrazine. The dimethyl analogue has been most fully investigated and a mono-lactam and its 2:4-dinitrophenylhydrazine derivative have been prepared as well as a di-derivative with phenylhydrazine in acetic acid.

Attempts to synthesise the dimethyl dilactone from β -methyltricarballic acid and acetic anhydride by established methods have not been successful nor have a number of other possible routes.

EXPERIMENTAL

1. Cyanoacetamide was prepared from ethylcyanoacetate and ammonia⁶³, recrystallised from ethanol and after drying at 100° for several hours to remove all traces of ammonia (cf. Kon and Thorpe²¹) it melted at 121°.
2. Diacetyl was prepared from the monoxime⁶⁴ by Olivier's method⁶⁵: a solution of diacetyl monoxime (101 grams; 1.0 mole) and sodium nitrite (170 grams; 2.0 moles) in water (2,800 mls.) was stirred and cooled to 15° while 18% sulphuric acid (540 mls.) was slowly added through a tube reaching to the bottom of the reaction vessel. After five days at room temperature the solution was saturated with anhydrous sodium sulphate, allowed to stand until the sodium sulphate decahydrate had crystallised and the aqueous layer decanted. The crystals were washed with a little cold water (50 mls.), the aqueous solution and washings distilled until no more diketone distilled with the water and the distillate then extracted with ether. After drying over sodium sulphate the extracts were evaporated at 60° to a yellow oil which was distilled to give diacetyl (66 grams; 76.7%), b.p. 86-88°.
3. Dibutyryl and dipropionyl were prepared by an adaptation of the method used by Ruggli and Zeller⁶⁶ to prepare several

diketones from the corresponding acyloins.

(a) A solution of propionoin⁶⁷ (17 grams; 0.147 moles) and methanol (7.5 mls.) in 70% aqueous acetic acid (870 mls.) was refluxed for $\frac{1}{2}$ hr. with cupric acetate (52.5 grams; 0.35 moles). The precipitated copper oxide was filtered, the filtrate neutralised with saturated sodium carbonate solution and then ether extracted. The combined extracts, after drying over sodium sulphate, were filtered and evaporated to a yellow oil which was distilled under reduced pressure to give dipropionyl (15.5 grams; 93%), b.p. 48-52°/13 mm.

(b) Dibutyryl (16.8 grams; 81%), b.p. 58-62°/13 mm., was prepared in the same way, using butyroin⁶⁷ (21.1 grams) in the place of propionoin.

4. Benzil was prepared from benzoin⁶⁸ by the method of Clark and Dreger⁶⁹:

A mixture of crystalline copper sulphate (410 grams), technical pyridine (400 grams) and water (160 mls.) was stirred on a steam-bath until solution was complete. Crude benzoin (169.6 grams) was added, the mixture heated and stirred for a further 2 hrs. and then cooled to solidify the oily product. The copper sulphate-pyridine solution was decanted from the crude benzil which was then treated with boiling 10% hydrochloric acid (150 mls.). After cooling and

filtering, the solid was recrystallised from carbon tetrachloride to give yellow needles of benzil (140 grams; 83%), m.p. 94-95°.

5. Ethyl 3-benzoyl-2-cyanocinnamate (cf. Bacher⁴³).

A solution of benzil (6.3 grams; 0.03 moles) in ethyl cyanoacetate (6.8 grams; 0.06 moles) was treated at 65° with piperidine (0.5 grams), and after 24 hrs. at 65-70° the solid product was extracted with a mixture of ether and ethanol (3:1; 200 mls.). After filtration the extract was evaporated on a water-bath and the yellow residue recrystallised from 70% aqueous ethanol to give colourless needles of the product (5 grams; 52.6%), m.p. 141°. Light absorption, λ_{\max} . 247 μ . ($\epsilon = 15,350$) and 285 μ . ($\epsilon = 11,890$) in ethanol, 5.85 μ . and 6.05 μ . in nujol.

6. 4-Cyano-2:3-diphenyl-2-hydroxy-5-oxo- Δ^3 -pyrroline

(a) A solution of benzil (41.9 grams; 0.2 moles) in ethanol (700 mls.) at 25° was stirred with a suspension of cyanoacetamide (16.7 grams; 0.2 moles) while piperidine (2.2 grams) was added dropwise. The resulting solution was refluxed for $\frac{1}{2}$ hr., evaporated to dryness under reduced pressure, the yellow residue washed with water and filtered to give a colourless solid which was recrystallised from 60% ethanol to yield colourless needles of the hydrate of 4-cyano-2:3-diphenyl-2-hydroxy-5-oxo- Δ^3 -pyrroline (31.7 grams;

88.8%), m.p. 170° . (Found: C, 69.9; H, 4.7; N, 9.4. $C_{17}H_{14}N_2O_3$ requires C, 69.4; H, 4.8; N, 9.5%). Light absorption λ_{\max} . 292 μ . ($\epsilon = 11,760$) in ethanol, 5.85 μ . in nujol.

(b) The hydrate, after recrystallisation from aqueous pyridine, gave colourless needles of the anhydrous product, m.p. 186° . (Found: C, 73.6; H, 4.7; N, 9.9. $C_{17}H_{12}N_2O_2$ requires C, 73.9; H, 4.4; N, 10.1%). Light absorption, λ_{\max} . 293 μ . ($\epsilon = 11,043$) in ethanol, 5.85 μ . in nujol.

(c) The hydrate (2 grams) was refluxed for 8 hrs. in benzene (20 mls.), the resulting colourless crystals filtered and recrystallised from benzene to yield the anhydrous product, m.p. $183-186^{\circ}$, undepressed by admixture with a specimen prepared as above.

(d) A similar procedure to that described above, using a solution of sodium (4.6 grams; 0.2 atoms) in ethanol (50 mls.) in the place of piperidine, led to a bright yellow solution which was poured into ice-cold 5 N. hydrochloric acid (200 mls.), diluted with water (500 mls.) and the resulting solid filtered to give a colourless product which was recrystallised from 60% aqueous ethanol as colourless needles of the hydrate (31.0 grams), m.p. 170° , undepressed by admixture with an authentic sample prepared as above.

(e) A solution of ethyl 3-benzoyl-2-cyanocinnamate (1 gram) in ethanol (30 mls.) was stood for 4 hrs. at 70° with concentrated aqueous ammonium hydroxide solution (sp. gr. 0.88; 7 mls.), the volatile fractions then evaporated under reduced pressure and the residue recrystallised from aqueous pyridine to give 4-cyano-2:3-diphenyl-2-hydroxy-5-oxo- Δ^3 -pyrroline (0.81 grams), m.p. 186°, undepressed by admixture with a sample prepared as above.

On recrystallisation from 60% aqueous ethanol the anhydrous compound gave the hydrate, m.p. 170°, undepressed by admixture with a specimen prepared as above.

7. 4-Cyano-2:3-diphenyl-2-ethoxy-5-oxo- Δ^3 -pyrroline

(a) The hydrate (1 gram) was refluxed for 15 mins. with ethanol (10 mls.) containing concentrated hydrochloric acid (2 mls.), the solvent then evaporated under reduced pressure and the residue recrystallised from ethanol to give colourless needles of 4-cyano-2:3-diphenyl-2-ethoxy-5-oxo- Δ^3 -pyrroline (0.86 grams), m.p. 184. (Found: C, 74.7; H, 5.3; N, 9.0. $C_{19}H_{16}N_2O_2$ requires C, 75.0; H, 5.3; N, 9.2%).

(b) A similar procedure using the anhydrous hydroxy-oxopyrroline (V) (1 gram) in the place of the hydrate, led to the same ethoxy derivative, m.p. 184°, undepressed by admixture with the specimen prepared above.

8. 4-Cyano-2:3-diphenyl-2-methoxy-5-oxo- Δ^3 -pyrroline

A similar procedure to that used for the ethoxy derivative was followed using methanol in the place of ethanol. The colourless residue, after evaporation of the solvent, was recrystallised from methanol to yield colourless needles of 4-cyano-2:3-diphenyl-2-methoxy-5-oxo- Δ^3 -pyrroline (0.84 grams), m.p. 194° . (Found: C, 74.3; H, 5.0; N, 9.2; OMe, 10.3. $C_{18}H_{14}N_2O_2$ requires C, 74.5; H, 4.8; N, 9.7; OMe, 10.7%). Light absorption, λ_{max} . 5.85 μ . in nujol.

9. 4-Cyano-2-hydroxy- and 4-cyano-2-methoxy-2:3-diphenyl-1-methyl-5-oxo- Δ^3 -pyrroline

(a) Dimethyl sulphate (3.78 grams; 0.03 moles) was shaken for 1 hr. with a cold solution of the hydrate (2.9 grams; 0.01 moles) in water (20 mls.) containing sodium hydroxide (1.32 grams; 0.03 moles). The precipitated solid was filtered, washed with 10% sodium hydroxide solution then water and recrystallised from 60% aqueous ethanol to yield colourless needles of 4-cyano-2:3-diphenyl-2-methoxy-1-methyl-5-oxo- Δ^3 -pyrroline (2.1 grams), m.p. 158° . (Found: C, 75.0; H, 5.4; N, 8.9; OMe, 12.9. $C_{19}H_{16}N_2O_2$ requires C, 75.0; H, 5.3; N, 9.2; OMe, 10.2%).

On acidifying the combined filtrate and washings with 10% sulphuric acid a solid precipitated and on

recrystallisation from 60% aqueous ethanol gave colourless needles of 4-cyano-2:3-diphenyl-2-hydroxy-1-methyl-5-oxo- Δ^3 -pyrroline (0.8 grams), m.p. 222°. (Found: C, 74.0; H, 4.6; N, 9.5; OMe, 2.8. $C_{18}H_{14}N_2O_2$ requires C, 74.5; H, 4.8; N, 9.7; OMe, Nil%). Light absorption, λ_{max} . 288 m μ . ($\epsilon = 11,690$) in ethanol.

(b) A similar procedure using the anhydrous (V) in the place of the hydrate led to the same mono- and dimethyl products, m.ps. 222° and 158° respectively, undepressed by admixture with the corresponding samples prepared from the hydrate.

10. 2-Acetoxy-1-acetyl-4-cyano-2:3-diphenyl-5-oxo- Δ^3 -pyrroline.

A solution of the hydrate (2 grams) in pyridine (20 mls.) containing acetic anhydride (6 grams) was refluxed for 10 mins. and the resulting red solution evaporated under reduced pressure to an oil which solidified on shaking with water. The crude product was recrystallised from 70% aqueous acetone to yield colourless needles of 2-acetoxy-1-acetyl-4-cyano-2:3-diphenyl-5-oxo- Δ^3 -pyrroline (1.15 grams; 47.0%), m.p. 159°. (Found: C, 70.2; H, 4.4; N, 7.8. $C_{21}H_{16}N_2O_4$ requires C, 70.0; H, 4.4; N, 7.8%).

11. α,α -Diphenylsuccinic acid (cf. Long and Miller⁴⁹).

Sodium (5.4 grams) was dissolved in ethanol (abs; 80 mls.), diphenylacetonitrile (19.4 grams) added and the

mixture refluxed for 1 hr. After cooling to 50° ethyl bromoacetate (25 grams) was added with stirring at such a rate as to cause gentle boiling of the ethanol, the mixture refluxed a further 3 hrs. and the volatile fractions then evaporated under reduced pressure. The dark residue was stirred with water (60 mls.) for $\frac{1}{2}$ hr., the resulting solid filtered and recrystallised from 95% ethanol to give colourless needles (22 grams), m.p. 101-105°. These were heated on a steam-bath for 15 mins. with a solution of potassium hydroxide (13 grams) in ethanol (95%; 100 mls.), the solution cooled to 0°, and the colourless sodium salt filtered. It was dissolved in water (80 mls.), the solution acidified with 5 N. hydrochloric acid, the colourless acid recrystallised from ethanol as needles (18 grams), m.p. 178°, and then refluxed for 68 hrs. with concentrated hydrochloric acid (200 mls.). The colourless product was filtered, washed with water, dissolved in 10% aqueous sodium hydroxide solution, then reprecipitated with 5 N. hydrochloric acid and recrystallised from ethanol to give α,α -diphenylsuccinic acid (12.6 grams; 67.1%), m.p. 170°. (Long and Miller give 173-175°).

12. α,α -Diphenylsuccinimide

(a) An authentic specimen was prepared from the acid by the method of Long and Miller (loc.cit.):-

A solution of α,α -diphenylsuccinic acid (4 grams)

in concentrated aqueous ammonium hydroxide solution (sp. gr. 0.88; 50 mls.) was evaporated on an oil-bath which was gradually raised to 210° . The residual oil was cooled, dissolved in boiling ethanol and the solution chilled to yield a colourless solid which after several recrystallisations from a benzene/petrol (40-60) mixture and from 50% aqueous ethanol gave α, α -diphenylsuccinimide (3.3 grams), m.p. $141-142^{\circ}$. Light absorption, λ_{\max} . 208 μ . ($\epsilon = 18,450$) in ethanol.

(b) The hydrate (1 gram) was refluxed for 2 hrs. with an excess of 15% aqueous sodium hydroxide solution (20 mls.), the colourless solution then cooled, acidified with 5 N. hydrochloric acid and the oily product extracted with ether. The extracts were washed, dried over sodium sulphate, evaporated to an oil which crystallised on standing and was recrystallised from 50% aqueous ethanol to yield colourless plates of α, α -diphenylsuccinimide (0.7 grams; 82.0%), m.p. $141-142^{\circ}$, undepressed by admixture with an authentic sample prepared as above. (Found: C, 76.3; H, 5.4; N, 5.2. Calculated for $C_{16}H_{13}NO_2$ C, 76.5; H, 5.2; N, 5.6%). Light absorption, λ_{\max} . 208 μ . ($\epsilon = 18,700$) in ethanol.

(c) The anhydrous hydroxy-oxo-pyrroline (V) (1 gram), hydrolysed in a similar way with 15% sodium hydroxide solution (20 mls.) yielded α, α -diphenylsuccinimide (0.7 grams), m.p. $141-142^{\circ}$ (from 50% aqueous ethanol), undepressed by admixture

with specimens prepared as above from α,α -diphenylsuccinic acid and from the hydrate.

13. α,α -Diphenyl-N-methylsuccinimide

(a) A solution of α,α -diphenylsuccinic acid (4 grams) in 25% aqueous methylamine solution (50 mls.) was distilled to dryness and the residue heated to 210° . After cooling the residue was recrystallised from ethanol to give α,α -diphenyl-N-methylsuccinimide (2.9 grams), m.p. $89-91^{\circ}$. (Long and Miller, loc.cit. give $88-90^{\circ}$).

(b) A cold solution of α,α -diphenylsuccinimide (0.5 grams; 0.02 moles), prepared from the hydrate as described above, in 5% aqueous potassium hydroxide solution (4.6 mls; 0.04 moles) was shaken for 5 hrs. with dimethyl sulphate (0.5 grams; 0.04 moles). The oily product, isolated by decanting the aqueous layer, solidified on washing with water and was recrystallised from ethanol to yield α,α -diphenyl-N-methylsuccinimide (0.2 grams; 37.7%), m.p. $88-90^{\circ}$, undepressed by admixture with an authentic sample prepared from α,α -diphenylsuccinic acid. (Found: C, 76.9; H, 5.9; N, 4.9. Calculated for $C_{17}H_{15}NO_2$ C, 77.0; H, 5.7; N, 5.3%).

14. Attempts to dehydrate 4-cyano-2:3-diphenyl-2-hydroxy-5-oxo- Δ^3 -pyrroline (V).

(a) Reaction with phosphorus pentoxide

The following procedure was adopted in several

attempts to effect dehydration using this reagent: A solution of either the hydrated or anhydrous (V) (0.01 moles) in dry benzene or dry chloroform (200 mls.) was stirred with a suspension of phosphorus pentoxide under the conditions tabulated below. After completion of the reaction ice-water (50 mls.) was added to the cooled stirred mixture, the organic layer evaporated under reduced pressure at 60°, the oily products solidified with ice, then filtered and recrystallised from aqueous pyridine. In some cases a little red pyridine-insoluble gum was produced, which did not solidify and was not further investigated.

Starting Material	Moles of P ₂ O ₅	Temp.	Time Hrs.	Solvent	Product		
					Grams	m.p.	Mixed m.p. with (V)
Hydrate	0.02	Room	2	Chloroform	2.3	184-186	184-186
(V)	0.01	Reflux	5	"	2.0	185-186	185-186
Hydrate	0.02	Room	6	"	2.4	185-186	186
(V)	0.10	Reflux	6	"	1.8	182-185	184-186
(V)	0.01	Reflux	2	Benzene	2.3	184-186	184-186
(V)	0.10	Reflux	6	"	2.3	186	186

(b) Reaction with phosphorus oxychloride

The hydroxy-oxo-pyrroline (V) or its hydrate (0.005 moles) was stirred and heated on an oil bath with pure phosphorus oxychloride (20 mls.), as tabulated below. The volatile fractions were then evaporated under reduced pressure and the residues shaken with water (10 mls.) to decompose any phosphorus oxychloride still present. The products, except under the mildest conditions when no reaction occurred, were all amorphous solids which could not be recrystallised. Analysis of some specimens after washing with ethanol, benzene and ether led to no satisfactory primary formulæ.

Starting Material	Temp.	Time	Product			
			m.p.	Analysis		
				C	H	N
(V)	65°C.	1 hr.	165-166 ^{o*}			
Hydrate	65°C.	6 hrs.	166 ^o *			
Hydrate	100°C.	6 hrs.	164-166 ^{o*}			
(V)	Reflux	15 mins.	Indefinite			
(V)	Reflux	30 mins.	>360 ^o	76.2	4.1	11.6
(V)	Reflux	1 hr.	>360 ^o			
Hydrate	Reflux	3 hrs.	>360 ^o	73.9	4.3	11.1

* These products were recrystallised from 60% aqueous ethanol and shown to be the hydrate by means of mixed melting points.

(c) Reaction with acetic anhydride

(i) The hydrate (1.4 grams) was ground to a paste with acetic anhydride (5 mls.), the mixture stood for 15 hrs. at room temperature with occasional mixing and exclusion of moisture, then stirred with ice/water (100 mls.) to decompose the anhydride. The resulting solid (1.36 grams) was recrystallised from aqueous pyridine to give 4-cyano-2:3-diphenyl-2-hydroxy-5-oxo- Δ^3 -pyrroline, m.p. 186°, undepressed by admixture with an authentic specimen.

(ii) The anhydrous hydroxy-oxo-pyrroline (V) (2.0 grams) was refluxed for 10 mins. in acetic anhydride (5 mls.) and the dark solution evaporated under reduced pressure to a black tarry residue. No solvent suitable for recrystallisation was discovered. A solution of the black residue (0.25 grams) in an ethanol/petrol (40+60^o) mixture (1:2; 5 mls.) was added to the top of an alumina column and eluted with the same mixture. No separation into bands was obtained, and similar experiments employing mixtures of acetone/petrol, ether/petrol, and ether/acetone were also unsuccessful. Fractions of 10 mls. were collected in all cases, but the only residues obtained after evaporation were black tars.

(d) Reaction with concentrated sulphuric acid

(i) Anhydrous (V) (1 gram) was stirred for 9 hrs. with cold concentrated sulphuric acid (20 mls.), the solution then poured into ice/water (70 mls.), the resulting colourless

solid filtered and washed with water. After recrystallisation from aqueous pyridine, unchanged (V) was obtained (0.86 grams), m.p. and mixed m.p. with an authentic sample 186° .

(ii) Anhydrous (V) (1 gram) was heated on a steam-bath for 2 hrs. with concentrated sulphuric acid (20 mls.) the red solution cooled and poured into water. The dark green solid could not be recrystallised.

(e) Reaction with polyphosphoric acids

Polyphosphoric acids were prepared by stirring 20 grams. of syrupy 85% phosphoric acid with the calculated quantity of phosphorus pentoxide. The temperature was kept below 80° by adding the oxide at a sufficiently slow rate. In this way acids containing up to 84% of phosphorus pentoxide were made. Stronger acids were prepared by adding the calculated amount of phosphorus pentoxide and then stirring at 180° for 15 mins. (cf. Bell⁵⁴).

The following procedure was adopted. The polyphosphoric acid (20 grams.) was adjusted to the reaction temperature, the hydrated or anhydrous (V) (1 gram) added with stirring and after completion of the reaction ice/water (150 mls.) was added. The yellow solids so obtained were recrystallised from 80% aqueous acetic acid. The results of analyses of some of them are detailed below:-

Starting Material	% P ₂ O ₅	Temp. °C.	Time Hrs.	Product			Empirical Formula	
				m.p. °C.	Analysis			
					C	H		N
(V)	70	120*	½	>360				
Hydrate	70	80	1	>360				
(V)	70	60	8	186‡				
Hydrate	80	120*	1	>360	70.4	4.5	11.3	C ₁₄ H ₁₁ N ₂ O ₂
Hydrate	80	80	3	>360				
Hydrate	80	60	10	186‡				
Hydrate	85	120**	1	>360	72.5	4.1	11.4	C ₁₆ H ₁₁ N ₂ O ₂
(V)	85	80	4	>360				
(V)	85	60 [‡]	12	>360	72.0	4.3	11.2	C ₁₅ H ₁₁ N ₂ O ₂
(V)	90	120 [‡]	1	>360				

* The initial temperature of 120° was allowed to fall spontaneously during the reaction.

** 5 mls. of redistilled phosphorus oxychloride were added to the reaction mixture.

‡ These products were recrystallised from aqueous pyridine and were shown by mixed melting points to be the anhydrous (V).

15. 4-Cyano-3-cyanoacetamido-2:3-dialkyl-2-hydroxy-5-oxopyrrolidines

(a) Diacetyl (10.75 grams; 0.125 moles) was added dropwise over $\frac{1}{2}$ hr. to a stirred solution of cyanoacetamide (21 grams; 0.25 moles) in ethanol (95%; 150 mls.) at 50-60°. After a further 2 hrs. at this temperature, the mixture was stood for 12 hrs. at room temperature, the precipitated solid then filtered, washed with ice-cold ethanol (10 mls.) and recrystallised from water to yield colourless prisms of 4-cyano-3-cyanoacetamido-2:3-dimethyl-2-hydroxy-5-oxopyrrolidine (26.5 grams; 90%), m.p. 289°. (Found: C, 50.8; H, 5.3; N, 24.0. $C_{10}H_{12}N_4O_3$ requires C, 50.8; H, 5.1; N, 23.8%).

(b) By substituting dipropionyl (12.75 grams; 0.125 moles) for diacetyl in the above reaction a colourless solid was obtained which was recrystallised from glycol to yield prisms of 4-cyano-3-cyanoacetamido-2:3-diethyl-2-hydroxy-5-oxopyrrolidine (16.27 grams; 49%), m.p. 325-326°. (Found: C, 54.3; H, 6.0; N, 21.0. $C_{12}H_{16}N_4O_3$ requires C, 54.6; H, 6.1; N, 21.2%).

(c) A solution of cyanoacetamide (16.8 grams; 0.2 moles) and dibutyryl (14.2 grams; 0.1 moles) in water (60 mls.) at room temperature was treated dropwise over 1 hr. with piperidine (2 grams) in water (20 mls.). After 49 hrs. the colourless solid was filtered and washed with water (5 mls.), to yield

colourless prisms of 4-cyano-3-cyanoacetamido-2:3-dipropyl-2-hydroxy-5-oxopyrrolidine (3.2 grams; 10.1%), m.p. 343°C . (from glycol). (Found: C, 57.8; H, 7.0; N, 19.1. $\text{C}_{14}\text{H}_{20}\text{N}_4\text{O}_3$ requires C, 57.5; H, 6.8; N, 19.1%).

16. 4-Cyano-3-cyanoacetamido-2:3-diphenyl-2-hydroxy-5-oxopyrrolidine

The hydrate of 4-cyano-2:3-diphenyl-2-hydroxy-5-oxo- Δ^3 -pyrroline (2.9 grams; 0.01 moles) was refluxed for 80 hrs. in ethanol (20 mls.) with cyanoacetamide (8.4 grams; 0.01 moles) and piperidine (1 ml.). The precipitated solid was filtered and purified by successive washings with boiling ether, acetone, ethanol and water to yield colourless crystals of 4-cyano-3-cyanoacetamido-2:3-diphenyl-2-hydroxy-5-oxopyrrolidine (1.9 grams; 53%), m.p. 426° . (Found: C, 66.7; H, 4.5; N, 15.1. $\text{C}_{20}\text{H}_{16}\text{N}_4\text{O}_3$ requires C, 66.7; H, 4.4; N, 15.5%).

17. 2:3-Disubstituted-3-carboxyacetamido-(or carboxycyanomethyl)-4-cyano-(or amido)-2-hydroxy-5-oxopyrrolidines
(XXV; R' = COOH, R'' = CN or CONH₂, R''' = CONH₂ or CN).

The oxopyrrolidines (1 gram) were dissolved with gentle warming in 90% sulphuric acid (11.5 mls.) and the solutions immediately cooled and stood for 24 hrs. After dilution with ice-water (25 mls.), the solutions were stood for 36 hrs., the colourless crystals filtered, washed with water and crystallised as indicated below. Thus were prepared:-

- (a) 2:3-dimethyl- (0.81 grams; 75%), m.p. 334° (from water).
(Found: C, 47.1; H, 5.4; N, 16.1; EW, 256. $C_{10}H_{13}N_3O_5$
requires C, 47.1; H, 5.1; N, 16.5%; EW, 255).
- (b) 2:3-Diethyl- (0.26 grams; 25%), m.p. $337-338^{\circ}$ (from aqueous
glycol). (Found: C, 51.0; H, 6.0; N, 14.6. $C_{12}H_{17}N_3O_5$
requires C, 50.9; H, 6.0; N, 14.8%).
- (c) The diphenyl-oxopyrrolidine gave by this method 2:3-
diphenyl-3-acetamido-(or cyanomethyl)-4-cyano-(or amido)-
2-hydroxy-5-oxopyrrolidine (0.47 grams; 51%), m.p. 338°
(from glycol). (Found: C, 68.1; H, 5.1; N, 12.4.
 $C_{19}H_{17}N_3O_3$ requires C, 68.1; H, 5.1; N, 12.5%).

18. Dilactones of β -acyl-(or benzoyl)- β -alkyl-(or phenyl)-
glutaric acids.

(a) (XXVIII; R = R' = Me)

The dimethyl-oxopyrrolidine (XXII; R = Me) (5 grams)
was refluxed for 24 hrs. with 8 N. sulphuric acid (20 mls.).
On cooling colourless plates formed which were filtered and
recrystallised from water to yield colourless plates of the
dilactone of β -acetyl- β -methylglutaric acid (3.43 grams; 95%),
m.p. 148° . (Found: C, 56.5; H, 5.8; E.W. 85.0. $C_8H_{10}O_4$
requires C, 56.5; H, 5.9%. E.W. 85.0).

(b) A similar reaction using the acid (XXV; R = Me, R' =
COOH, R'' = CN or CONH₂, R''' = CONH₂ or CN) (1 gram) and 8 N.
sulphuric acid (5 mls.) led to colourless plates of the same

dilactone (0.62 grams), m.p. 148° , undepressed by admixture with an authentic sample prepared as above.

(i) 2:4-dinitrophenylhydrazine derivative

A solution of the dilactone (0.5 grams) in ethanol (95%; 5 mls.) was heated at 100° for 10 mins. with 2:4-dinitrophenylhydrazine (0.3 grams), concentrated hydrochloric acid (0.5 mls.) then added and on dilution with water a yellow solid precipitated. This on recrystallisation from 60% aqueous ethanol yielded the 2:4-dinitrophenylhydrazone (1.0 grams; 97%), m.p. 256° . (Found: C, 48.0; H, 3.8; N, 15.7. $C_{14}H_{14}N_4O_7$ requires C, 48.0; H, 4.0; N, 16.0%).

(ii) lactam-lactone

A solution of the dilactone (1 gram) in ethanol (5 mls.) and concentrated ammonium hydroxide (sp. gr. 0.88; 5 mls.) was refluxed for 2 hrs. then evaporated to dryness under reduced pressure and the residue recrystallised from benzene to yield the lactam-lactone of β -acetyl- β -methyl-glutaric acid (0.8 grams; 83%), m.p. $187-188^{\circ}$. (Found: C, 56.9; H, 6.3; N, 8.4. $C_8H_{11}NO_3$ requires C, 56.8; H, 6.5; N, 8.2%).

(iii) lactam-2:4-dinitrophenylhydrazone

a) A solution of the lactam-lactone (0.3 grams) in ethanol (2 mls.) was refluxed for 10 mins. with 2:4-dinitrophenylhydrazine (0.3 grams), concentrated hydrochloric

acid (0.5 mls.) then added, the solution diluted with water and the precipitated product recrystallised from 60% aqueous ethanol to yield the lactam-2:4-dinitrophenylhydrazone, m.p. 300-308°. (Found: C, 44.6; H, 3.9; N, 18.7. $C_{14}H_{15}N_5O_8$ requires C, 44.1; H, 3.9; N, 18.4%).

b) The 2:4-dinitrophenylhydrazone (0.3 grams) in ethanol (2 mls.) was refluxed for 1 hr. with concentrated ammonium hydroxide solution (sp. gr. 0.88; 5 mls.), the solution evaporated to dryness under reduced pressure and the residue recrystallised from 60% aqueous ethanol to give yellow crystals of the lactam-2:4-dinitrophenylhydrazone, m.p. 300-308°, undepressed by admixture with the sample prepared above.

(iv) Bis-phenylhydrazine derivative

A solution of the dilactone (1 gram; 0.06 moles) and phenylhydrazine (1.3 grams; 0.12 moles) in glacial acetic acid (10 mls.) was refluxed for 8 hrs. the acetic acid removed under reduced pressure and the residue recrystallised from methanol to give the bis-phenylhydrazone (1.7 grams; 87%), m.p. 232-233°. (Found: C, 68.2; H, 6.2; N, 15.9. $C_{20}H_{22}N_4O_2$ requires C, 68.5; H, 6.3; N, 16.0%).

(c) (XXVIII; R = R' = Et)

The diethyl-oxopyrrolidine (XXII; R = Et) (5 grams) was refluxed for 24 hrs. with 8 N. sulphuric acid (20 mls.),

the cooled solution extracted with ether and the extracts dried over sodium sulphate. After evaporation of the ether the residue was recrystallised from water to give colourless needles of the dilactone of β -ethyl- β -propionylglutaric acid (3.56 grams; 95%), m.p. 100° . (Found: C, 60.5; H, 7.3; E.W. 98.8. $C_{10}H_{14}O_4$ requires C, 60.6; H, 7.1%; E.W. 99.0). The impure 2:4-dinitrophenylhydrazone had m.p. 228-239 $^{\circ}$.

(d) (XXVIII; R = R' = Pr)

In the same way, using the dipropyl-oxopyrrolidine (XXII; R = Pr) (2.5 grams) and 8 N. sulphuric acid (20 mls.), there was obtained after recrystallisation from water, the dilactone of β -butyryl- β -propylglutaric acid (0.86 grams; 90%), m.p. 88-89 $^{\circ}$. (Found: C, 63.9; H, 7.8; E.W. 112. $C_{12}H_{18}O_4$ requires C, 63.7; H, 8.0%; E.W. 113). 2:4-Dinitrophenylhydrazone, m.p. 235-238 $^{\circ}$ (from 60% aqueous ethanol). (Found: C, 52.8; H, 5.4; N, 14.3. $C_{18}H_{22}N_4O_7$ requires C, 53.2; H, 5.4; N, 13.8%).

(e) (XXVIII; R = R' = Ph)

A solution of the diphenyl-oxopyrrolidine (XXII; R = Ph) (10 grams) in 80% sulphuric acid (100 mls.) was refluxed for 36 hrs. the mixture diluted with water and the product extracted with ether. The extracts were dried (sodium sulphate), evaporated on a water-bath and the residue recrystallised from 40% aqueous ethanol to give the dilactone

of β -benzoyl- β -phenylglutaric acid (0.63 grams; 10%), m.p. 203-204°. (Found: C, 73.3; H, 4.9; E.W. 147. $C_{18}H_{14}O_4$ requires C, 73.4; H, 4.8%; E.W. 147).

19. Preparation of β -methyltricarballic acid

(a) Ethyl α -cyano- β -methylglutaconate (cf. Rogerson and Thorpe²⁴).

A solution of sodium (11.5 grams) in ethanol (250 mls.) was evaporated to dryness at 190° and 8 mm. pressure. The sodium ethoxide was allowed to cool in vacuo and then treated with ethyl cyanoacetate (56.5 grams) followed by ethyl acetoacetate (65 grams). The mixture was heated on a steam-bath for $\frac{1}{2}$ hr. then cooled, dissolved in water (300 mls.), acidified with 5 N. hydrochloric acid and the precipitated oil extracted with ether. After washing and drying the extracts over sodium sulphate, the ether was evaporated and the oily residue fractionated under reduced pressure to give ethyl α -cyano- β -methylglutaconate (58 grams; 51.5%), b.p. 170-172°/27 mm.

(b) Ethyl α, β -dicyano- β -methylglutarate (cf. Hope and Sheldon⁷⁰).

A solution of ethyl α -cyano- β -methylglutaconate (45 grams) in ethanol (95%; 250 mls.) was treated with a solution of potassium cyanide (26 grams) in water (150 mls.), cooled to 0° C. and then dropwise with stirring with 20%

hydrochloric acid (3 moles). After 15 mins. at room temperature the mixture was poured into 5 N. hydrochloric acid (1 litre), the precipitated oil extracted with ether, the extracts washed with 10% sodium bicarbonate solution and dried over sodium sulphate. After evaporation of the ether the residue was fractionated under reduced pressure to give ethyl α, β -dicyano- β -methylglutarate (36.8 grams; 73%), b.p. 184-188°/14 mm.

(c) β -methyltricarballic acid (cf. Hope and Sheldon, loc.cit.).

The above dicyano-ester (36.8 grams) was refluxed with concentrated hydrochloric acid (300 mls.) until a clear solution was obtained (about 15 hrs.), the solution then evaporated to dryness under reduced pressure and the solid residue extracted in a Soxhlet extractor with dry ether for 4 days. After evaporation of the ether the residue was recrystallised from formic acid to give β -methyltricarballic acid (16.1 grams; 58%), m.p. 162-164°.

20. Attempts to prepare the dilactone of β -acetyl- β -methylglutaric acid from β -methyltricarballic acid.

(a) β -Methyltricarballic acid (3.8 grams; 0.02 moles) was added to a cold solution of sodium (1.38 grams; 0.06 atoms) in ethanol (abs; 50 mls.), the ethanol then evaporated under reduced pressure and the residue dried in vacuo over

phosphorus pentoxide. The sodium β -methyltricarballylate so prepared was heated for 72 hrs. at $130-140^{\circ}$ with re-distilled acetic anhydride (3.1 grams; 0.03 moles), the excess anhydride then evaporated under reduced pressure and the dark brown residue treated as follows:-

- (i) Extracted with boiling ether. On evaporation of the extracts no residue was obtained.
- (ii) Extracted with boiling benzene. On evaporation of the extracts there was no residue.
- (iii) Extracted with boiling chloroform. No residue was obtained on evaporation of the extracts.
- (iv) The residue was dissolved in water (50 mls.) and acidified with 5 N. hydrochloric acid. The solution was evaporated to dryness under reduced pressure and the residue extracted several times with boiling ether. On evaporation of the ether the extracts yielded pure β -methyltricarballylic acid (3.68 grams), m.p. $162-164^{\circ}$, undepressed by admixture with an authentic sample.

(b) Sodium- β -methyltricarballylate (5.12 grams; 0.02 moles) prepared as above was refluxed for 18 hrs. with redistilled acetyl chloride (25 mls.), the volatile fractions evaporated under reduced pressure and the residue extracted with (i) boiling ether, (ii) boiling chloroform, and (iii) boiling benzene. None of the extracts yielded any product on

evaporation. The extracted solid was dissolved in water (10 mls.), the solution acidified with 5 N. hydrochloric acid, then evaporated to dryness and the colourless residue extracted with boiling ether. This extract was evaporated to dryness to give a colourless solid which was recrystallised from formic acid to yield β -methyltricarballylic acid (3.71 grams), m.p. and mixed m.p. with an authentic sample 162-164°.

(c) β -Methyltricarballylic acid (3.8 grams; 0.02 moles) was refluxed for 8 hrs. in acetic anhydride (25 mls.), the excess anhydride then evaporated under reduced pressure and the residue (3.8 grams) recrystallised from formic acid to give unchanged β -methyltricarballylic acid, m.p. and mixed m.p. with an authentic specimen 162-164°.

(d) Potassium β -methyltricarballylate (6.08 grams; 0.02 moles), prepared similarly to the sodium salt using potassium ethoxide and β -methyltricarballylic acid, was heated for 72 hrs. at 130-140° with acetic anhydride (9.3 grams; 0.09 moles). Extraction as before yielded no product and the residue was converted by dilute hydrochloric acid as before into β -methyltricarballylic acid (3.1 grams), m.p. 162-164° (from formic acid), undepressed by admixture with an authentic sample.

(e) Ammonium β -methyltricarballylate (4.82 grams;

0.02 moles), prepared by reduced pressure evaporation of a solution of the acid (3.8 grams) in concentrated ammonium hydroxide solution (sp. gr. 0.88; 20 mls.), similarly yielded unchanged β -methyltricarballic acid, m.p. and mixed m.p. with an authentic specimen 162-164^o, after reaction with acetic anhydride (9.3 grams; 0.09 moles) at 130-140^o for 72 hrs.

21. Ethyl acetylmethylmalonate (cf. Michael⁷¹).

Sodium (6.9 grams; 0.3 atoms) was dissolved in ethanol (abs; 150 mls.) and the solution evaporated to dryness at 190^o, the last traces of ethanol being removed at 5 mm. pressure. The foam of sodium ethoxide was allowed to cool in vacuo, a solution of ethyl methylmalonate⁷² (52.2 grams; 0.3 moles) in dry benzene (200 mls.) then added followed by dropwise addition of a solution of acetyl chloride (23.08 grams; 0.294 moles) in dry benzene (100 mls.) accompanied by vigorous stirring. After the addition was complete the mixture was refluxed for $\frac{1}{2}$ hr. then cooled, stirred with ice/water (100 mls.) containing concentrated sulphuric acid (2 mls.), and the benzene layer separated. The aqueous layer was extracted once with benzene, the combined benzene solutions dried over sodium sulphate and after evaporation of the solvent the residue was fractionated under reduced pressure. After a considerable amount of low-boiling fore-run

the product distilled at 130-132°/18 mm. (27.7 grams; 35%), (Found: C, 55.6; H, 7.3. Calculated for $C_{10}H_{16}O_5$ C, 55.6; H, 7.4%).

22. Attempts to prepare acetylmethylmalonic acid from the di-ethyl ester

(a) Hydrolysis with aqueous sodium hydroxide

Ethyl acetylmethylmalonate (5 grams) was refluxed with 15% aqueous sodium hydroxide solution (30 mls.) until a clear solution was obtained, and the cooled solution then treated with the equivalent volume of 2 N. hydrochloric acid. The water was then evaporated in a stream of warm dry air, the residue extracted with boiling ethanol, the sodium chloride filtered and the ethanol evaporated under reduced pressure to give an oily residue which solidified on standing. After recrystallisation from ethyl acetate/petrol (40-60°) colourless needles of methylmalonic acid (1.64 grams; 60%) were obtained, m.p. 133-134°, undepressed by admixture with an authentic sample prepared from ethyl methylmalonate in the same way.

(b) Hydrolysis with ethanolic sodium hydroxide

Ethyl acetylmethylmalonate (5 grams) was refluxed for $\frac{1}{2}$ hr. in ethanol (abs. 50 mls.) with sodium hydroxide (5.2 grams), the ethanol then evaporated under reduced pressure, the residue dissolved in water and treated with

the equivalent amount of 2 N. hydrochloric acid. The solution was then evaporated to dryness in a stream of warm dry air, the residue extracted with boiling ethanol and the filtered extract evaporated to dryness under reduced pressure. The residue was recrystallised from ethylacetate/petrol (40-60°) to give colourless needles of methylmalonic acid (1.8 grams; 66%), m.p. 133-134°, undepressed by admixture with an authentic sample prepared as above from ethyl methylmalonate.

23. 3:3-bis-hydroxymethyl-butan-2-one (cf. Holmes and Morgan⁶⁰).

A mixture of 40% aqueous formaldehyde solution (225 grams), ethyl-methyl-ketone (108 grams) and 2 N. aqueous sodium hydroxide solution (25 mls.) was warmed until a vigorous reaction commenced. When this had subsided the solution was refluxed for $\frac{1}{2}$ hr., the water evaporated under reduced pressure on a steam-bath and the viscous residue distilled at 20-60 mm. pressure to a temperature of 250°. The colourless distillate was redistilled under reduced pressure and the fraction, b.p. 138-142°/15 mm. (23 grams) was collected. It solidified on standing and was recrystallised from chloroform/petrol (40-60°) to give needles of the product (18.5 grams), m.p. 60°.

24. Experiments with 3:3-bis-hydroxymethyl-butan-2-one

(a) Reaction with concentrated hydrochloric acid

A solution of the dihydroxyketone (5 grams) in cold concentrated hydrochloric acid (25 mls.) was stirred for 72 hrs., the cloudy mixture then diluted with ice/water (100 mls.) and extracted with ether. The extracts were washed, dried over magnesium sulphate and evaporated to a pale yellow oil which distilled without apparent fractionation (through a twelve inch column packed with Fenske spirals) between 40 and 85°/25 mm. A sample b.p. 80-85°/25 mm. was analysed. (Found: C, 43.6; H, 6.8; Cl, 24.9. $C_6H_{11}ClO_2$ requires C, 47.8; H, 7.3; Cl, 23.6%). It therefore appeared that only one of the hydroxy groups had reacted.

(b) Reaction with anhydrous hydrogen chloride

Dry hydrogen chloride gas was passed for 4 hrs. into a solution of the dihydroxyketone (5 grams) in dry ether (150 mls.), the mixture allowed to stand for a further 24 hrs. and then evaporated at 50° under reduced pressure to an oil which decomposed to a black tar on attempting to distill it at 15 mm.

(c) Reaction with anhydrous hydrogen bromide

The dihydroxyketone (5 grams) was stood for 24 hrs.

in solution in ether (150 mls.) saturated with anhydrous hydrogen bromide. The volatile fractions were then evaporated at 50° under reduced pressure and the dark residual oil distilled under reduced pressure to give a pale yellow oil (3.6 grams), b.p. 108/5 mm. (Found: Br, 40.3. $C_6H_{11}BrO_2$ requires Br, 41.0%). (Déscombe⁶¹ reported that reaction with hydrogen bromide led to an oil, b.p. 106-107°/2 mm.).

(d) Reaction with p-toluene sulphonyl chloride

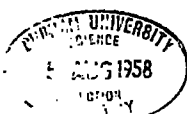
The dihydroxyketone (2.64 grams; 0.02 moles) was added to an ice-cold solution of p-toluene sulphonyl chloride (7.62 grams; 0.04 moles) in dry pyridine (10 mls.). After 2 hrs. at 0° the mixture was kept at room temperature for 18 hrs. and then poured into ice/water (200 mls.) containing concentrated sulphuric acid (2 mls.). The viscous oil was isolated by decanting the aqueous layer and dissolved in chloroform. The chloroform solution was washed with water, dried over magnesium sulphate and evaporated to a colourless oil.

A solution of this oil in dry acetone (50 mls.) was heated to 90° for 10 hrs. in a sealed tube with sodium iodide (6 grams), dry ether (50 mls.) then added, the solid filtered and the solvents evaporated to yield a colourless oil which did not distill at 0.2 mm.

REFERENCES

1. Wurtz, Jber.Fortschr.Chem., 1872,449.
2. Idem., Compt.rend., 1878,87,45.
3. Schmidt, Chem.Ber., 1880,13,2342.
Claison, ibid., 1881,14,2468.
4. Kyriakides, J.Amer.chem.Soc., 1914,36,534.
5. Claison, Chem.Ber., 1890,23,977.
6. Knoevenagel, Ann., 1894,281,25; Chem.Ber., 1904,37,4461.
7. Idem., Chem.Ber., 1898,31,2596.
8. Komppa, ibid., 1900,33,3530.
9. Sen Gupta, J.chem.Soc., 1921,119,298.
10. Heuch, Chem.Ber., 1895,28,2251.
11. Dornow and Wiehler, Ann., 1952,578,113.
12. Linstead and Williams, J.chem.Soc., 1926,2735.
13. Harding, Haworth, and Perkin, ibid., 1908,93,1943.
14. Ingold, ibid., 1921,119,329.
15. Boxer and Linstead, ibid., 1931,740.
16. Doedner, Chem.Ber., 1900,33,2140.
Haworth, Rankin, and Perkin, J.chem.Soc., 1924,125,1693.
17. Guareschi, Mem.R.Accad.Sci.Torino., 1901-1902,50,235;
Atti.R.Accad.Sci.Torino., 1900-1901,36,443.
ibid., 1910,1911,46,622; Chem.Zbl., 1899,118.
18. Guareschi, and Grande, ibid., 1899,439.
Squintanyi, Atti.R.Accad.Sci.Torino., 1912-1913,48,675.

19. Guareschi, ibid., 1901-1902, 37, 593.
20. Thole and Thorpe, J.chem.Soc., 1911, 99, 422.
Thorpe and Wood, ibid., 1913, 103, 1586.
21. Kon and Thorpe, ibid., 1919, 115, 686.
22. Day and Thorpe, ibid., 1920, 117, 1465.
23. Curtis, Day, and Kimmins, ibid., 1923, 123, 3131.
24. Rogerson and Thorpe, ibid., 1905, 87, 1685.
25. Corson and Kohler, J.Amer.chem.Soc., 1923, 45, 1975.
26. Ingold, "Structure and Mechanism in Organic Chemistry",
G. Bell and Sons Ltd., London, 1953, pages 680-685.
27. Hann and Lapworth, J.chem.Soc., 1904, 85, 47.
28. Bardhan, ibid., 1929, 2223; ibid., 1930, 1509.
29. Wagtendonc and Weiburg, Rec.Trav.chim.Pays-Bas., 1942, 61, ⁷²⁸
30. Basu, J.Indian chem.Soc., 1930, 7, 815.
31. Ingold, J.chem.Soc., 1930, 184.
32. Barat, J.Indian chem.Soc., 1930, 7, 321; ibid., 1931, 8, 699.
33. Errera, Chem.Ber., 1900, 33, 2969.
34. Sen Gupta, J.chem.Soc., 1915, 107, 1347.
35. Cooper, Ingold, and Ingold, ibid., 1926, 1868.
36. Beilstein, Vol. III, 1, 676.
37. Wolff, Ann., 1885, 229, 260.
38. Lukes, Coll.Trav.chim.Tchécosl., 1929, 1, 119.
Lukes, and Prelog, ibid., 1929, 1, 282, 334, 461, 617.



39. Walton, J.chem.Soc., 1940, 438.
40. Hill and Lutz, J.org.Chem., 1941, 6, 175.
41. Bāshour and Lindwall, J.Amer.chem.Soc., 1935, 57, 178.
42. Davison and Japp, J.chem.Soc., 1895, 67, 132.
43. Bāchér, J.prakt.Chem., 1929, 120, 301.
44. Druey and Schmidt, Helv.chim.acta., 1954, 37, 134.
45. Coenen and Pestener, Z.Electrochem., 1953, 57, 785.
46. Browne and Lutz, J.org.Chem., 1953, 18, 1638.
47. Bellamy "The Infra-Red Spectra of Complex Molecules",
Methuen and Co. Ltd., London, 1954.
48. Weissberger, "Techniques of Organic Chemistry, Vol. IX",
Interscience Publishers Ltd., London, 1956.
49. Long and Miller, J.Amer.chem.Soc., 1951, 73, 4895.
50. Biltze and Rimpel, Chem.Ber., 1908, 41, 1379.
51. Ingold, "Structure and Mechanism in Organic Chemistry",
G. Bell and Sons Ltd., London, 1953, page 480.
52. Eby and Hauser, J.Amer.chem.Soc., 1957, 79, 729.
53. Snyder and Werker, ibid., 1950, 72, 2962.
54. Bell, Ind.Eng.Chem., 1948, 40, 1464.
55. Brady, J.chem.Soc., 1931, 756.
56. Emery, Ann., 1897, 295, 123.
57. Fittig and Roth, ibid., 1901, 314, 16.
58. Fittig and Salomon, ibid., 1901, 314, 92.

59. McEwen and Mehta, J.Amer.chem.Soc., 1953, 75, 240.
60. Holmes and Morgan, J.chem.Soc., 1932, 2667.
61. Descombe, Compt.rend., 1936, 203, 1077.
62. Baer and Fischer, J.Amer.chem.Soc., 1948, 70, 609.
63. Corson, Scott and Vose, Org.Synth., Coll.Vol.I, page 179.
64. Damerell and Semon, ibid., Coll.Vol.II, page 204.
65. Olivier, Bull.Soc.Chim., 1932, 51, 99.
66. Ruggli and Zeller, Helv.chim.acta., 1945, 28, 741.
67. McElvain and Snell, Org.Synth., Coll.Vol.II, page 114.
68. Adams and Marvel, ibid., Coll.Vol.I, page 94.
69. Clarke and Dreger, ibid., Coll.Vol.I, page 87.
70. Hope and Sheldon, J.chem.Soc., 1922, 121, 2227.
71. Michael, Amer.chem.J., 1892, 14, 510.
72. Cox and McElvain, Org.Synth., Coll.Vol.II, page 279.