Kinetics and Mechanism of the Condensation Reaction of Symmetrical and Unsymmetrical 1,3-Diketones with Cyanoacetamide in the Synthesis of 4,6-Disubstituted-3-cyano-2-pyridones

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The rate constants for the condensation reaction of cyanoacetamide with pentane-2,4-dione, 5methylhexane-2,4-dione and 5,5-dimethylhexane-2,4-dione catalysed by piperidine were determined under a variety of experimental conditions. A UV spectrophotometric method for rate measurements was developed and the structures of the products were elucidated by means of a spectroscopic study. On the basis of the obtained rate constants, activation parameters and the evidence on the structure of synthesized unsymmetrical 4,6-disubstituted-3-cyano-2-pyridones a possible reaction scheme was suggested. It was thus possible to explain the selectivity of the reaction and the position of substituents in the pyridones obtained.

The condensation of 1,3-dicarbonyl compounds with derivatives of cyanoacetic acid is among the most common methods for the synthesis of pyridines from acyclic components. It has been applied to numerous 1,3-dioxo compounds, and proceeds under mild conditions in good to excellent yields.¹ The original Guareschi-Thorpe synthesis of 3-cyano-4,6-dimethyl-2-pyridone^{2,3} has been further extended to the study of the reaction conditions and selectivity when unsymmetrical 1,3-diketones are involved.⁴ The general conclusion was that the more polarised carbonyl reacts first and that the substituent attached to it occupies position 4 in the pyridine nucleus.¹ It was also suggested that in discussions considering the orientation of this reaction, steric effects should be taken into account.⁵ At this stage it was extensively discussed whether the mechanism of this condensation reaction is a Knoevenagel condensation or a Michael addition, which is irrelevant from the point of view of electronic effects, although the extent of enolisation of 1,3diketones⁶ favours the second option. It is probable that an interplay of both electronic and steric effects determines the ratio of the two possible isomers.

It seems that investigations of this reaction were abandoned for a long period. However, in the last decade there has been renewed interest in substituted pyridones and related compounds,⁷⁻¹¹ no doubt due to the discovery of their cardiotonic and antidiabetic activity. Although to our knowledge not a single compound of this type has been commercialised, it seems that a considerable amount of research is in progress.

Our own investigations in this field include preliminary studies on the selectivity in the synthesis of 4,6-dialkyl-3-cyano-2-pyridones involving unsymmetrical 1,3-diketones,12 development of a UV spectrophotometric method and preliminary kinetics experiments ^{13,14} and the effect of catalysts.¹⁵ We also synthesized a number of new 4(6)-methyl-6(4)-(substituted phenyl)-3-cyano-2-pyridones, which were the subject of an NMR study on the orientation in this reaction, based on the ratio of isomers.^{16,17} New and improved methods for the synthesis of known and unknown compounds of this type with potential physiological activity have been developed.¹⁸ Spectral characteristics of two series of 4,6-disubstituted-3-cyano-2pyridones, namely methyl-alkyl and methyl-substituted phenyl, have recently been recorded, and the corresponding ¹H chemical shifts and IR and UV frequencies correlated with a variety of LFER parameters.¹⁹

In this paper we present the results of an investigation of the

kinetics of the base-catalysed reaction of cyanoacetamide with acetylacetone (pentane-7,4-dione), isobutyrylacetone (5-meth-ylhexane-2,4-dione) and acetylpinacolone (5,5-dimethylhexane-2,4-dione).

Results and Discussion

Kinetic Data .--- Rate data for the piperidine-catalysed reactions of cyanoacetamide with pentane-2,4-dione, 5-methylhexane-2,4-dione and 5,5-dimethylhexane-2,4-dione are given in Tables 1, 3 and 4, respectively. The kinetics were studied at equimolar concentrations of reactants and catalyst, Tables 1(a), 3(a) and 4(a), and the corresponding rate constants satisfactorily calculated from the second-order rate law. The experiments were also performed at an excess of both reactants and catalyst, and the results for acetylacetone are presented in Tables 1(b), 1(c) and 1(e) (excess of cyanoacetamide and catalyst in the same run). In the reaction of unsymmetrical diketones, isobutyrylacetone and acetylpinacolone, excess of cyanoacetamide and catalyst was employed and the corresponding rate data are presented in Tables 3(b), 3(c) and 4(b), 4(c), respectively. Pseudo-first-order kinetics are indicated in these experiments, and the rate constants are calculated accordingly. Table 2 presents the activation parameters for the reaction of pentane-2,4-dione at three temperatures. The reaction of the symmetrical diketone has been more extensively studied, in comparison with the other two, because of the higher reaction rate, the formation of only one isomer, and the absence of a steric factor.

All rate constants presented were calculated on the basis of the increase in the concentration of the product, the corresponding 3-cyano-2-pyridone. It is evident from the UV spectra in Fig. 1 that the decrease of diketone concentration could also be monitored, but it was established that the absorption maxima are subject to changes in both position and intensity with changing piperidine concentration. No such interference was observed for the products, substituted 3-cyano-2-pyridones. Also, perturbations due to reversible diketone selfcondensation could be visualised.

We believe that the investigated reaction can be conveniently represented by Scheme 1. It is usually considered ²⁰ that for this kind of base-catalysed process, broadly described as carbanion addition to a carbonyl function, which includes many reactions such as Claisen, Michael and Perkin condensations, there is an

 $k_2(\text{stat})/10^2 \text{ dm}^6 \text{ mol}^{-2} \text{ s}^{-1}$

2.71 ^e

3.87 ^f

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Table 1 Rate constants^a for the piperidine-catalysed reaction of acetylacetone (AA) with cyanoacetamide (CAA)

(a) Equimolar concentra	tions of reactants a	nd catalyst		
$c_{\rm AA}, c_{\rm CAA}, c_{\rm PIP}/{ m mol}~{ m dm}^{-3}$	$k_2/dm^3 \text{ mol}^{-1} \text{ s}^{-1}$	$k_2(\text{average})/\text{dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$	-1	
0.01	0.49			
0.02	0.49	0.51		
0.03	0.51	0.51		
0.04	0.55			
(b) Excess of acetylaceto	ne			
$c_{CAA}, c_{PIP}/mol dm^{-3}$	$c_{AA}/mol dm^{-3}$	$k_1/10^{-5} \mathrm{s}^{-1}$	$k_2(\text{stat})/10^{-5}\text{dm}^3\text{mol}^{-1}\text{stat}$	-1
0.02	0.1	6.66		
0.02	0.2	12.36	co coh	
0.02	0.3	16.56	58.62	
0.02	0.4	24.8		
(c) Excess of cyanoaceta	mide			
$c_{\rm AA}, c_{\rm PIP}/{ m mol}~{ m dm}^{-3}$	$c_{\rm AA}/{ m mol}~{ m dm}^{-3}$	$k_1/10^{-5} \mathrm{s}^{-1}$	$k_2(\text{stat})/10^{-5}\text{dm}^3\text{mol}^{-1}\text{s}^{-1}$	
0.02	0.10	10.14		
0.02	0.15	16.8	115.06	
0.02	0.20	20.7	115.0	
0.02	0.25	27.8		
(d) Excess of piperidine				
$c_{AA}, c_{CAA}/mol dm^{-3}$	$c_{\rm PIP}/{ m mol}~{ m dm}^{-3}$	$k_1/10^{-3} \text{ s}^{-1}$	$k_2(\text{stat})/10^{-5}\text{dm}^3\text{mol}^{-1}\text{s}$	-1
0.02	0.1	9.65		
0.02	0.2	12.48	25 (1)	
0.02	0.3	16.17	33.01	
0.02	0.4	20.29		
(e) Excess of cyanoaceta	mide and of piperic	line		
$c_{\rm AA}/{ m mol}~{ m dm}^{-3}$	c _{CAA} /mol dm ⁻³	$c_{\rm PIP}/{ m mol}~{ m dm}^{-3}$	$k_1/10^{-5} \text{ s}^{-1}$	$k_2/10^{-5} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$
0.008	0.1	0.02	20.6	206.4
0.008	0.1	0.04	32.0	320.0
0.008	0.1	0.08	42.0	420.0
0.008	0.1	0.12	52.0	520.0
0.008	0.1	0.16	60.3	603.0
0.008	0.2	0.02	32.7	163.5
0.008	0.2	0.04	57.8	289.0
0.008	0.2	0.06	60.0	360.0
0.008	0.2	0.08	83.6	418.0
^a Calculations based on ^c r = 0.99, intercept = -	the increase in py -1.43×10^{-5} , s.d. =	ridone concentration. ^b r = 7.4×10^{-5} , $n = 4.k_{2}$ (ave	= 0.99, intercept = $4.4 \times$ erage) = 0.98. ^d r = 0.99. in	10^{-6} , s.d. = 7.6 × 10^{-5} , <i>n</i> therefy = -1.43×10^{-5}

 $h = 4. k_2(\text{average}) = 0.54.$ $h, \text{ s.d.} = 4.6 \times 10^{-5}, n = 4.$ $K_{eq}(average) = 1.1 \times 10^{-3}$. $e_r = 0.99$, intercept = 1.86 $\times 10^{-3}$, $\tilde{s.d.} = 1.57 \times 10^{-3}$, n = 5. $f_r = 0.96$, intercept = 9.9 $\times 10^{-4}$, $s.d. = 1.04 \times 10^{-3}$, $n = 1.04 \times 1$ n = 4.

Table 2 Activation parameters^a for the reaction of acetylacetone with cyanoacetamide at three different temperatures

<i>T</i> /°C	Rate constants/s ⁻¹	E‡/ kJ mol⁻¹	log A	ΔS [‡] (60 °C) J K ⁻¹ mol ⁻¹
50 60	0.34 0.55 }	41.5	6.27	-142.3
70	0.94]			

^{*a*} Values of E^{\ddagger} and ΔS^{\ddagger} are accurate to within 10 kJ mol⁻¹ and 1.0 J K⁻¹ mol-1 respectively.

initial equilibrium between one of the reactants and a basic catalyst followed by a slow reaction of the anion formed, with the other reagent.

If the same reasoning is applied to the investigated reaction, it follows that the active intermediate cyanoacetamide anion (CAA⁻) is formed in the fast equilibrium (1) between the cyanoacetamide (HCAA) and piperidine (PIP), and that in step (2) it reacts with acetylacetone (AA) yielding the intermediate

$$HCAA + PIP \xrightarrow{k_1} CAA^- + PIPH^+$$
(1)

$$CAA^{-} + AA \xrightarrow{k_{2}} PY^{-} - I \qquad (2)$$

 PY^{-} – I. Therefore, both reagents and the catalyst must appear in the rate equation. Preliminary investigations showed that the kinetics are very complex, and that experiments at equimolar concentrations only, could not give an insight into the reaction mechanism. Therefore experiments were performed at a variety of reaction conditions, regarding concentrations and temperature. Results obtained under pseudo-first-order conditions, and presented in Tables 1(b), 1(c) and 1(d), for the reaction of acetylacetone, show that the variation of the concentration of both reactants and the catalyst affects the reaction rate. Thirdorder kinetics could have been expected, as has been established for similar reactions.21

It should be noted, however, that this reaction proceeds at low concentrations of reactive species, considering that cyanoacetamide is a weak acid and the diketone is enolised and



Scheme 1

 Table 3 Rate constants^a for the piperidine-catalysed reaction of isobutyrylacetone (IBA) with cyanoacetamide

(a) Equimolar c	oncentrations of r	eactant and cataly	st
c _{IBA} , c _{CAA} , c _{PIP} /mol dm ⁻³	$\frac{k_2}{\mathrm{mol}^{-1}} \mathrm{s}^{-1}$	k ₂ (aver- age)/dm ³ mol ⁻¹ s ⁻¹	
0.07	0.062		
0.08	0.068	0.065	
0.085	0.065		
(b) Excess of cya	inoacetamide		
$c_{\rm IBA}, c_{\rm PIP}/\rm{mol}$			$k_{2}(\text{stat})/10^{-5}$
dm ⁻³	$c_{AA}/mol \ dm^{-3}$	$k_1/10^{-5} \text{ s}^{-1}$	dm ³ mol ⁻¹ s ⁻¹
0.016	0.08	1.08	
0.016	0.12	1.75	12.16
0.016	0.16	2.00	13.1°
0.016	0.22	2.99	
(c) Excess of pip	eridine		
$c_{\rm IBA}, c_{\rm AA}/{\rm mol}$			$k_{2}(\text{stat})/10^{-5}$
dm ⁻³	$c_{\rm PIP}/{ m mol}~{ m dm}^{-3}$	$k_1/10^{-5} \text{ s}^{-1}$	dm ³ mol ⁻¹ s ⁻¹
0.08	0.12	2.05	
0.08	0.16	2.46	12.66
0.08	0.20	3.06	12.6
		2	

^{*a*} Calculated from the increase in pyridone concentration. ^{*b*} r = 0.99, intercept = 5.3 × 10⁻⁷, s.d. = 7.9 × 10⁻⁶, n = 4. k_2 (average) = 0.056 dm³ mol⁻¹ s⁻¹. ^{*c*} r = 0.99, intercept = 5.03 × 10⁻⁶, s.d. = 5.08 × 10⁻⁶, n = 3. $K_{eg} = 2.44 \times 10^{-3}$.

subject to self-condensation,¹ which leads to a highly complex kinetic behaviour. A possible approach could be to apply a steady state approximation^{22,23} considering that in the equilibrium (1) most probably $k_{-1} \gg k_2$ [AA], from which follows eqn. (3). Since [PIPH⁺] is consumed in the subsequent fast

$$k_{1}[\text{HCAA}][\text{PIP}] = k_{-1}[\text{CAA}^{-}][\text{PIPH}^{+}] + k_{2}[\text{CAA}^{-}][\text{AA}] \quad (3)$$

step, and [PIP] is regenerated, the steady state concentration of [CAA] is given by eqn. (4) and the rate of the reaction is

$$[CAA^{-}]_{ss} = \frac{k_{1}[HCAA][PIP]}{k_{-1} + k_{2}[AA]}$$
(4)

 Table 4 Rate constants^a for the piperidine-catalysed reaction of acetylpinacolone (AP) with cyanoacetamide

(a) Equimolar c) Equimolar concentrations of reactant and catalyst				
c _{AP} , c _{CAA} , c _{PIP} /mol dm ⁻³	k_2/dm^3 mol ⁻¹ s ⁻¹	$k_2(\text{aver-} \text{age})/\text{dm}^3$ mol ⁻¹ s ⁻¹			
0.02	0.054				
0.04	0.056 }	0.055			
(b) Excess of cya	anoacetamide				
c _{AP} , c _{PIP} /mol dm ⁻³	$c_{AA}/mol dm^{-3}$	$k_1/10^{-5} \mathrm{s}^{-1}$	$k_2(\text{stat})/10^{-5}$ dm ³ mol ⁻¹ s ⁻¹		
0.02	0.2	2.16			
0.02	0.4	3.32	cach		
0.02	0.6	4.3	5.35 °		
(c) Excess of pip	peridine				
$c_{\rm AP}, c_{\rm CAA}/{\rm mol}$			$k_2(\text{stat})/10^{-5}$		
dm ⁻³	c _{PIP} /mol dm⁻³	$k_1/10^{-5} \text{ s}^{-1}$	dm ³ mol ⁻¹ s ⁻¹		
0.02	0.12	0.96			
0.02	0.20	1.33			
0.04	0.20	1.6	6.3		

^{*a*} Calculated from the increase in pyridone concentration. ^{*b*} r = 0.99, intercept = 1.12×10^{-5} , s.d. = 1.07×10^{-5} , n = 3. k_2 (average) = 0.063 dm³ mol⁻¹ s⁻¹. ^{*c*} r = 0.90, intercept = 2.0×10^{-6} , s.d. = 3.2×10^{-6} , n = 3. $K_{eq} = 1.37 \times 10^{-3}$.

apparently unimolecular in both reactants and the catalyst [eqn. (5)]. The rate constant is evidently a composite one, and

rate =
$$\frac{k_1}{k_{-1}} k_2$$
[CAA][AA][PIP] =
 k_{obs} [CAA][AA][PIP] (5)

it should be expected, theoretically, that the reaction should conform to a third-order rate law. However, rate data for four equimolar concentrations of the reagents and catalyst, presented in Table 1(*a*) for acetylacetone, fitted the second-order rate equation very well, with correlation coefficients in the range 0.997–0.999. This could have been expected as the catalyst concentration is essentially constant, as piperidine is recovered in the fast step which follows the formation of the active intermediate $PY^- - I$ [eqn. (2) and step III in Scheme 1]. Therefore, we felt it justified to apply the relationship $1/c_{\infty} - c_{t_{e}}$.



Fig. 1 UV spectra for the reaction of acetylacetone with cyanoacetamide catalysed by piperidine at 0.03 mol dm⁻³ concentrations of reactants and catalyst

vs. time, for the calculation of the rate constants given in Table 1.1, for the reaction of acetylacetone, and also in Tables 3.1 and 4.1 for isobutyrylacetone and acetylpinacolone, respectively. Our decision was further supported by the reaction order determined for the reactions at equimolar concentrations of 0.02 and 0.03 mol dm⁻³. The value calculated ²⁴ from the corresponding half-lives is 1.88, which is 94% of the theoretical value.

The experiments performed under pseudo-first-order conditions, yielded the rate constants given in Table 1(b)-(d). The second-order rate constant calculated from these data, varied and also differed from the directly determined values in Table 1(a). This was not unexpected, considering the complex kinetic behaviour.

It was reasonable to suppose that the rate constants in Table 1(d), obtained at high piperidine concentrations and constant concentration of the reactants, should also be composite rate constants offering the possibility of calculating the equilibrium constant $K_{eq} = k_1/k_{-1}^{22}$ derived from the integrated form of eqn. (3), for low concentrations of acetylacetone and $k_2 \ll k_{-1}$. The equilibrium constant calculated in this manner has an average value of $K_{eq} = k_1/k_{-1} = 1.1 \times 10^{-3}$.

If this value is inserted into the rate equation of the form of eqn. (6) using the data in Table 1(b), for an excess of

$$k_{\rm obs} = k_2 K[AA] \tag{6}$$

acetylacetone, the obtained average value $k_2 = 0.54 \text{ dm}^3 \text{ mol}^{-1}$ s⁻¹ is very close to the second-order rate constants in Table 1(*a*). When the same treatment was applied to the observed rate constants at an excess of cyanoacetamide, given in Table 1 (*c*), an average rate constant of $k_2 = 0.98 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ is obtained, which is almost double the one obtained from the pseudo-first-order rate constants for an excess of acetylacetone. This is not suprising, as the ratio of the calculated second-order rate constants from Tables 1(*b*) and 1(*c*) is the same. These findings, however, show that an excess of cyanoacetamide is critical in the equilibrium step, and that under these conditions, the partitioning of the reactive intermediate CAA⁻ favours the reaction with acetylacetone, rather than the reverse step of the equilibrium. This proves the proposal of the slow step of the reaction, which is also corroborated by the data in Table 1. Rate constants obtained with an excess of both cyanoacetamide and piperidine are dimensionally apparently third order, but follow first-order kinetics. This is not unknown²⁰ and unexpected, considering the high excess of cyanoacetamide. However, the rate constant at double cyanoacetamide concentration is only 1.4 times higher, no doubt because the catalyst is recovered in the step which follows the slow step of the reaction.³ Further kinetic proof that the rate-determining step is the actual attack of the cyanoacetamide anion at the diketone molecule is the larger effect of the increase of the reaction rate at an excess of acetylacetone [Table 1(*b*)] than the effect of piperidine [Table 1(*d*)]. Acetylacetone participates only in the second step of the reaction and hence the slow step as indicated.

The activation parameters given in Table 2 also support the proposition of a slow second step as the activation energy and particularly high negative value of the entropy change indicate the requirements for specific orientation in the transition state, which it is only possible to visualize in the second step.

Rate data for the condensation reaction of 5-methylhexane-2,4-dione (isobutyrylacetone) and 5,5-dimethylhexane-2,4-dione given in Tables 3 and 4, respectively, do not show entirely the same kinetic pattern as those for acetylacetone condensation. The determined second-order rate constants given in Tables 3(a) and 4(a) show that the reactions are much slower, by almost one order of magnitude. This is logical, considering the orientation of the reaction discussed in the following section and the steric hindrance. The equilibrium constants are higher, although not excessively, but the calculated second-order rate constants are surprisingly close to the values obtained by direct measurement, although calculated from the pseudo-first-order rate constants with an excess of cyanoacetamide. This is not in agreement with the results for acetylacetone, considering that the equilibrium constants refer to the same reaction. The possible explanation could be that in the rate-determining step only the steric hindrance is the limiting factor, regardless of the concentration of the active intermediate and the values of the equilibrium constants are apparent values.

Stereochemical Data (Selectivity).—Of the three investigated diketones, acetylacetone yields a single product, but the two unsymmetrical ones, isobutyrylacetone and acetylpinacolone in the base-catalysed reaction with cyanoacetamide could give two

 Table 5
 Typical kinetic run^a

t/min	A	$c_{\rm pyr}/10^{-5}$ mol dm ⁻³	$\frac{(c_{\infty} - c_l)^{-1}}{\mathrm{dm}^3 \mathrm{mol}^{-1}}$
0	0.026	0.54	8 726
60	0.240	2.36	10 373
120	0.410	3.78	12 165
180	0.540	4.86	14 000
240	0.620	5.53	15 456
300	0.690	6.11	16 977
360	0.810	7.00	20 445
	1.120	9.69 ^b	43 290

^{*a*} $k_2 = 0.51 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$, r = 0.991, intercept = 8486, s.d. = 4017, n = 7. c_{AA} , c_{CAA} , $c_{PIP} = 0.03 \text{ mol dm}^{-3}$, $\lambda = 329 \text{ nm}$, $c_0^{UV} = 12 \times 10^{-5} \text{ mol dm}^{-3}$. (Initial concentration of reactants at UV measurement). Rate constants were reproducible to within $\pm 10\%$. ^{*b*} 75% conversion.

positional isomers. However, in practice only one product is formed. Analysis of the IR, NMR and MS spectra showed that the bulkier alkyl groups, isopropyl and *tert*-butyl, preferentially occupy position 4 in the pyridone nucleus. This is not in agreement with the statement that the bulkier alkyl group is found at the 6 position, although a mixture of isomers is usually obtained.¹ Judging by the difference in the polar²⁵ and steric substitutent constants²¹ for the methyl and *tert*-butyl groups, one should expect the steric effect to be dominant. Therefore, it was evident that the solution should be sought elsewhere.

The orientation in the investigated condensation reaction could be explained by the enolisation of the reacting diketone. The most favourable conformation of 1,3-diketones is the one where the carbonyl groups are as distant as possible. If bulky substituents are present, the diketone enolises more readily than attaining the less favourable conformation.⁶ An NMR study showed that the enol contribution increases with the branching of the alkyl substituents, the content of the enol form being 81% for methyl and 93% for the tert-butyl group.²⁶ Although these data refer to neat liquids and are different for ethanol solutions, and are probably also affected by piperidine concentration, the methyl/isopropyl and methyl/tert-butyl ratios must be similar. On the other hand, the IR spectra of 1,3-diketones in the enol form show an abnormal carbonyl absorption. This was attributed to intramolecular hydrogen bonding, the single-bonded structure being stabilised by resonance.⁶ Whenever intramolecular hydrogen bonding is significant, the hydrogen atom is a constituent of a six-membered planar ring, where all the other members have π -electrons associated with them.²⁷ Therefore, in the investigated reaction, the position of the nucleophilic attack is determined by the relative destabilisation of the two competing carbonyls. If the concept of hyperconjugation is assumed, the methyl group is a better electron donor than the isopropyl or tert-butyl groups, and, hence, orientation as observed. An attack of the nucleophile on the delocalised hydrogen bonded structure of the 1,3-diketone could be visualised, as shown in Scheme 1.

Mechanism.—The mechanism of the investigated reaction appears at first sight to be fairly straightforward, although the literature data indicate that both polar and steric effects influence the structure of the reaction products, *i.e.* the ratio of isomers.^{5,17} As far as we know, the present paper, together with earlier communications,^{13–15} put forward the only evidence on the kinetics of this reaction. The data from preliminary investigations are included in this work. It was established that the kinetic pattern is fairly complex, which is particularly true for the effect of the catalyst, as can be seen from the data given in the preceding section. If the catalyst and the cyanoacetamide concentration are critical for the formation of the active carbanion nucleophile, the polar and steric effects inherent to 1969

the diketone molecule determine the stability of the transition state and the intermediate addition complex. In solving this complex situation, several points should be taken into account.

The reaction of all three investigated diketones conforms strictly to the second-order rate law. No side or parallel reactions were observed and the reaction proceeds to relatively high yields under fairly mild conditions. Furthermore, it has been reported ⁵ that the reaction proceeds with a low concentration of reacting molecules. 1,3-Diketone is a stronger acid than the cyanoacetamide, and in base catalysis, only a low concentration of the ionised species is present. However, the carbonyl groups of the diketone are more polarised than the amide function of the cyanoacetamide and the diketone is an acceptor of the nucleophilic attack. It is most probable that the self-condensation of the diketone also occurs, but this is a reversible reaction, while the formation of the active intermediate is probably irreversible.

From this evidence, it is reasonable to postulate that the reaction proceeds as presented in Scheme 1. The initial fast equilibrium (step I) yielding the carbanion nucleophile is probably well shifted to the left $(k_1 \ll k_{-1})$ which is followed by the slow attack of the nucleophile at the delocalised diketone structure (step II), and the dominating component k_2 of the composite overall rate constant is the measure of the rate in the slow step of the reaction. The proposal for the slow step is further corroborated by the high negative value of ΔS^{\ddagger} , which indicates the requirements for a particular orientation of the reacting molecules in the transition state. Therefore, the evidence for the rate-determining step is both kinetic and stereochemical. The preequilibrium is fast, but shifted to the left. There is always enough of the highly reactive cyanoacetamide anion, but the steric requirements slow down the reaction, and hence the slow step. The subsequent protonation-dehydration and cyclisation steps (III and IV) are probably fast equilibria shifted strongly to the right and the last step (V), finally yielding ing a stable delocalised pyridone structure, is undoubtedly irreversible.

Experimental

Analytical Method for the Measurement of the Kinetics.--An analytical method was developed for the study of the kinetics of the reaction of 1,3-diketones and cyanoacetamide catalysed by bases. It was established that in the UV region 200-400 nm it is possible to record both the decrease of the diketone concentration and the increase of the concentration of the pyridone reaction product, as cyanoacetamide and the catalyst piperidine do not absorb in the above region of the UV spectra. Although an excellent isosbestic point ($\lambda = ca.$ 295 nm) was observed, it was not possible to calculate the rate constants from the decrease in the diketone concentration, for the reasons given in the discussion. A typical UV spectrum of the reaction is presented in Fig. 1. The concentrations were calculated from the straight line calibration equations. A typical kinetic run is given in Table 5. The corresponding UV diagram and concentration/ time relationship are given in Figs. 1 and 2, respectively. Characteristic UV absorption maxima were very nearly the same for all the three investigated 1,3-diketones, 273 nm, and for the pyridone reaction products 329 nm. All experiments were done in absolute ethanol.

Rate Measurements.—Reaction mixtures of diketone, cyanoacetamide and catalyst (concentrations *ca.* 10^{-2} mol dm⁻³) in absolute ethanol were placed in 6–10 stoppered test tubes (4–5 cm³) and immersed in an ultrathermostat water bath, kept at a preset temperature. Except for the determination of activation parameters (Table 2), the reaction temperature was 60 °C in all experiments. At the appropriate time intervals, the reaction



Fig. 2 Plot of reversal concentrations vs. time for the reaction of acetylacetone with cyanoacetamide catalysed by piperidine at 0.03 mol dm-3 concentrations of reactants and catalyst

mixture portions in individual test tubes, were quenched in icewater and diluted to spectrophotometric concentrations of the order of 10⁻⁵ mol dm⁻³. The spectrophotometer used was a Varian Superscan 3.

The choice of the concentrations of the reactants, particularly for the experiments performed under pseudo-first-order conditions, was determined by the limitations of the analytical procedure. The excess concentration of acetylacetone (λ_{max} = 273) had to be low enough not to absorb excessively at $\lambda = 329$ nm, the absorption maximum of the product pyridone. On the other hand, cyanoacetamide should not crystallize from the reaction mixture.

Materials .- Acetylacetone, piperidine (Fluka), cyanoacetamide (Riedel-de-Haen) and absolute ethanol (Zorka, Sabac, Yugoslavia) were reagent grade commercial products and used without further purification. Isobutyrylacetone 28,29 and acetylpinacolone 30-32 were synthesized by known procedures.

Synthesis of New Compounds.-4-tert-Butyl-6-methyl-3cyano-2-pyridone. Prepared by the standard Guareschi-Thorpe method.³ Equimolar quantitites (0.028 mol dm⁻³) of acetylpinacolone (4 g) and cyanoacetamide (2.4 g) were dissolved in a sufficient quantity of warm 96% ethanol (50 cm³) so that the cyanoacetamide did not crystallise on cooling. Piperidine (0.5 cm³) was added to the warm solution, which became warmer, and the precipitate formed almost immediately. Recrystallisation from ethanol gave white crystals, m.p. 220 °C (Found: C, 69.7; H, 7.35; N, 14.9. $C_{11}H_{14}N_2O$ requires: C, 69.47; H, 7.36; N, 14.73%). $v_{max}(KBr)/cm^{-1}$ 2227 (CN), 1632 (CO), 2600–3200 (NH).³³ The structure of the compound was confirmed by ¹H NMR and MS spectra. δ (CDCl₃) 2.47 (6-CH₃), 6.15 (5-H); m/z41, M - 41, M - 15. The structure was corroborated by the ¹³C NMR spectral data. The ¹H NMR spectrum of the crude product indicated small quantities (less than 10%) of the other positional isomer.

4-Isopropyl-6-methyl-3-cyano-2-pyridone. Synthesised as above from 0.7 g of isobutyrylacetone (4.0 \times 10^{-3} mol) and piperidine (0.3 cm³) and 0.68 g of cyanoacetamide (equimolar). Recrystallisation from ethanol, gave white crystals, m.p. 208-210 °C (Found: C, 68.4; H, 6.9; N, 16.0; $C_{10}H_{12}N_2O$ requires: C, 68.16, H, 6.86; N, 15.90%). $v_{max}(KBr)/cm^{-1}$ 2217 (CN), 1645 (CO) 2500–3200 (NH).³³ The structure of the compound was confirmed by the ¹H NMR and MS spectra δ (CDCl₃) 2.49 (6-CH₃), 6.13 (5-H); m/z 41, M – 41, M – 15. The structure was further corroborated by the ¹³C NMR spectral data. ¹H NMR spectra of the crude product indicated small quantities (ca. 7%) of the other positional isomer.

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