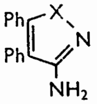
854. *Heterocyclic Derivatives of Guanidine. Part III.*[1] *Stoicheiometry and Kinetics of the Condensation of Ethyl Cyanoacetate with Guanidino-2*H*-pyrroles.*

By J. E. Banfield.

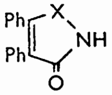
Guanidines are displaced in the above reactions by a nucleophilic addition followed by prototropic changes and an elimination. The kinetics are complex, the order in ethyl cyanoacetate being non-integral, and an interpretation based upon a rate-determining elimination step is presented.

Previous attempts (not reported) to establish the stoicheiometry of the reaction [2] of 5-guanidino-2-imino-3,4-diphenyl-2*H*-pyrrole [represented in formula I; X = (a); R = R′ = H; by one of its tautomeric forms [2]] with ethyl cyanoacetate by accounting for the atoms of the guanidino-residue were abortive. However, application of methods found successful in another problem to the analogous reaction of the piperidine analogue [I; X = (a); R = H; NR_2' = piperidino] with ethyl cyanoacetate in acetic acid now establish that 1-amidinopiperidine is formed along with the compounds [II and III; X = (d)]; compound [II; X = (d)] had not earlier [1] been detected in the reaction of these components in the absence of acetic acid; its formation is attributed to partial hydrolysis of the imino-compound to the lactam [II; X = (a); R = H, NR_2' = piperidino]. Reaction of this with ethyl cyanoacetate in acetic acid gave 1-amidinopiperidine.

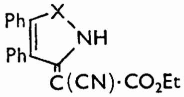
(I)

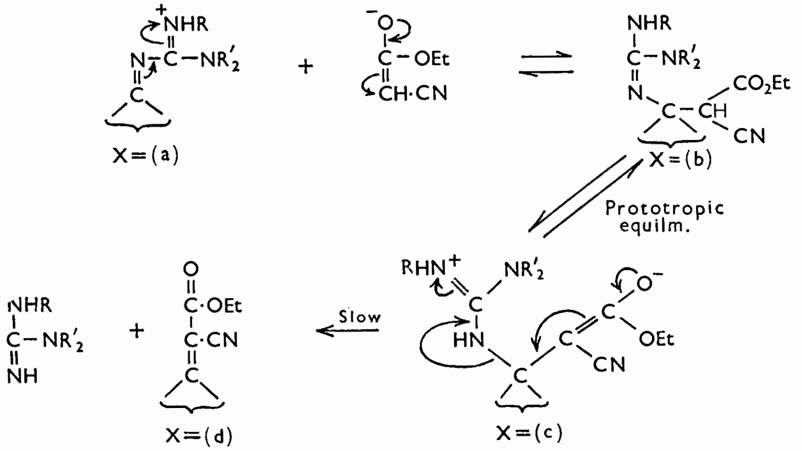


(II)



(III)





Scheme (a)

Accordingly, in view of the evolution of ammonia noted [2] when 2-imino-3,4-diphenyl-5-oxo-3-pyrroline reacted with ethyl cyanoacetate, it seemed likely that ammonia and/or the guanidine is displaced in a nucleophilic reaction of the protonated pyrrole derivative by (presumably) the cyanoacetate carbanion or enol. Qualitative attempts to demonstrate basic catalysts in these reactions by addition of an excess of sodium acetate to the above mixtures were not successful; apparent lack of basic catalysis might suggest participation

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[1] Part II, *J.*, 1961, 2098.
[2] Part I, *J.*, 1960, 2108.

of the enol or anion of ethyl cyanoacetate in an aldol condensation mechanism[3] as exemplified in scheme (a).

Preliminary attempts to follow the kinetics of the above reactions were not encouraging until a compound [II; X = (a); R = Me, R′ = Me] was prepared in the course of another investigation (cf. the Experimental section). Although the ultraviolet absorption of the oxopyrrole is of similar character to that of known compounds of this type, it is distinguished from them by being hypsochromically displaced, thus more readily permitting spectroscopic study of the kinetics of its reaction with ethyl cyanoacetate. Further, this oxopyrrole was soluble in ethanol (unlike some of the compounds described earlier) to a convenient degree. The reaction was rather slow, except at or near the boiling point of ethanol, and therefore was followed under reflux, although with some resultant loss of precision; some runs at 66° gave good first-order coefficients but were inconveniently slow.

EXPERIMENTAL

Reaction of 1-N′-(2-*Oxo*-3,4-*diphenyl*-2H-*pyrrol*-5-*yl*)*amidinopiperidine Nitrite with Ethyl Cyanoacetate*.—A mixture of this salt (1·0 g.), ethyl cyanoacetate (0·7 ml.), and acetic acid (2 ml.) was refluxed for 2 hr., diluted with methanol, and cooled, to yield 2-(α-cyano-α-ethoxycarbonylmethylene)-5-oxo-3,4-diphenyl-3-pyrroline (0·25 g.) which (from ethanol) had m. p. 165—169°. The mother-liquor was basified with sodium carbonate and treated with sodium picrate, giving 1-amidinopiperidine picrate, m. p. 151—152° (Found: C, 40·5; H, 4·8. Calc. for $C_{12}H_{16}N_6O_7$: C, 40·45; H, 4·5%).

Reaction of 1-N′-(2-*Imino*-3,4-*diphenyl*-2H-*pyrrol*-5-*yl*)*amidinopiperidine with Ethyl Cyanoacetate*.—The pyrrole (2·0 g.) gave, by the above method (½ hour's refluxing), 2,5-di-(α-cyano-α-ethoxycarbonylmethylene)-3,4-diphenyl-3-pyrroline (1·5 g.), m. p. and mixed m. p. 253—254·5° (from butan-1-ol), and 1-amidinopiperidine picrate (1·3 g.), m. p. 251—253° (Found: C, 40·6; H, 4·7%). The mother-liquors gave a solid (0·3 g.) which by chromatography on alumina afforded 2-(α-cyano-α-ethoxycarbonylmethylene)-5-oxo-3,4-diphenyl-3-pyrroline (0·19 g.), m. p. 163—164° (Found: C, 73·0; H, 4·65; N, 8·6. Calc. for $C_{21}H_{16}N_2O_3$: C, 73·2; H, 4·7; N, 8·1%).

2-*Cyanomethylene*-5-*oxo*-3,4-*diphenyl*-3-*pyrroline*.—2-α-Cyano-α-ethoxycarbonylmethylene-5-oxo-3,4-diphenyl-3-pyrroline (0·4 g.) was warmed to 30° with ethanolic-aqueous sodium hydroxide. The mixture, set aside for 2 days and then acidified, gave the *nitrile* (134 mg.), m. p. 197·5—198·5° (from ethanol), which when dried at 150°/0·01 mm. lost less than 2% by weight (Found: C, 79·3; H, 4·46; N, 10·2; O, 6·4. $C_{18}H_{12}N_2O$ requires C, 79·4; H, 4·4; N, 10·3; O, 5·9%), $\lambda_{max.}$ 318 mμ (log ε 4·419 in EtOH).

2-*Imino*-3,4-*diphenyl*-5-NNN′-*trimethylguanidino*-2H-*pyrrole*.—*NNN*′-Trimethylguanidinium sulphate was prepared from *NS*-dimethylisothiouronium sulphate and dimethylamine and afforded the picrate, m. p. 150·5—152° (lit., 151—152°). This sulphate (6·3 g.), sodium (0·9 g.), and *trans*-αβ-dicyanostilbene (7 g.) yielded, by the general method[2] after several days at 50° and then at room temperature, a yellow solution which on evaporation gave a brown oil. This was taken up in benzene and then yielded the crude pyrrole (7·0 g.). Recrystallisation of this from hot solvents caused decomposition unless the time of heating was kept at a minimum: even so slight colour developed. From acetone the *pyrrole* separated in yellow needles, m. p. 210° (decomp.) (Found: C, 72·05; H, 6·3; N, 20·2. $C_{20}H_{21}N_5$ requires C, 72·5; H, 6·4; N, 21·1%). From ethyl methyl ketone it was obtained in yellow prisms, m. p. 209° (decomp.) (Found: C, 72·1; H. 6·2; N, 20·5%). In 95% ethanol it had $\lambda_{max.}$ 304, $\lambda_{infl.}$ 354, 237, 227 mμ (log ε 4·288, 3·28, 4·24, 4·30) changed by acetic acid to $\lambda_{max.}$ 303, $\lambda_{infl.}$ 357, 250 mμ (log ε 4·262, 3·28, 4·08); both spectra are of type E.[2]

2-*Oxo*-3,4-*diphenyl*-5-NNN′-*trimethylguanidino*-2H-*pyrrole*.—The foregoing 2-imino-compound (1·5 g.) in ethanolic-aqueous acetic acid was treated with sodium nitrite (4 g.) and the product refrigerated for 2 months, filtered from a trace of green solid, and basified with sodium hydroxide solution, giving the *dihydrate*, m. p. 252° (decomp.), of the oxopyrrole (Found: C, 64·1; H, 6·4; N, 14·75. $C_{20}H_{20}N_4O,2H_2O$ requires C, 65·2; H, 6·6; N, 15·2%). This, recrystallised from ethanol, afforded the *oxopyrrole* in yellow prisms, m. p. 258—259° (decomp.) (Found: C, 72·2;

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[3] (*a*) Ingold, "Structure and Mechanism in Organic Chemistry," Bell, London, 1953, p. 284; (*b*) Barton, McCapra, May, and Thudium, *J.*, 1960, 1298.

H, 6·0; N, 16·5, 17·0; O, 5·5. $C_{20}H_{20}N_4O$ requires C, 72·3; H, 6·1; N, 16·9; O, 4·8%), $\lambda_{max.}$ 298, 230, $\lambda_{infl.}$ 340 mμ (log ε 4·309, 4·300, 3·32 in 95% EtOH), changed by alkali to $\lambda_{max.}$ 299, $\lambda_{infl.}$ 340, 228 mμ (log ε 4·314, 3·41, 4·33) (both of type E^2) and by acetic acid to $\lambda_{max.}$ 360, 277, $\lambda_{infl.}$ 250 mμ (log ε 3·738, 4·196, 4·133) (type I^2).

The oxopyrrole was heated in ethyl cyanoacetate, giving 2-α-cyano-α-ethoxycarbonylmethylene-5-oxo-3,4-diphenyl-3-pyrroline, m. p. and mixed m. p. 169—170° (from ethanol).

Kinetic Experiments.—Materials. Ethanol was dried by refluxing it with sodium ethoxide and diethyl phthalate and was then fractionally distilled. In some experiments, where rigorous dryness was not maintained, ethanol (commercial, absolute) was purified by fractionation. Triethylamine was fractionated from sodium.

Toluene-*p*-sulphonic acid was prepared from the monohydrate by dehydration at 100° under reduced pressure, then under an oil-pump vacuum, and was then made up in ethanol and standardised alkalimetrically.

Sodium ethoxide solution was freshly prepared and was standardised acidimetrically after dilution with water.

The oxopyrrole was made up in ethanol and aliquot parts of a stock solution were used.

Method. 2-Oxo-3,4-diphenyl-5-*NNN'*-trimethylguanidino-2*H*-pyrrole, ethyl cyanoacetate, and any additional materials were measured volumetrically, made up to 50·0 ml., and placed in a flask fitted with a ground-glass stopper, reflux condenser, stoppered side arm, and protecting tube, all of which had been kept at 115° overnight before assembly. When the solution was refluxing and was adjudged to have reached dynamic equilibrium (thermal), a sample was removed and cooled, and its optical density was measured on a Unicam S.P. 500 spectrophotometer (at least three readings; *D* usually ±0·001). Further samples were removed and measured at timed intervals. Temperatures measured with a thermometer immersed in the boiling liquid varied from 78·8° to 80·2°; in the Tables the values 79·5° is arbitrarily given. Runs at 66·05° were carried out conventionally in stoppered flasks.

TABLE 1. *First-order rate coefficients (min.*$^{-1}$*) of the reaction between ethyl cyanoacetate* (CA), *and* 2-*oxo*-3,4-*diphenyl*-5-NNN'-*trimethylguanidino*-2H-*pyrrole* (OP) *in ethanol.*

Run	Temp.	10^5[OP]	10^3[CA]		10^3k_1 (obs.)	10^3k_1 (calc.)	*R*[f]
16	79·5°	5·22	752		5·31	5·55	4·83
9	,,	13·1	376		4·50	4·85	4·18
12	,,	5·22	,,		3·94	3·93	,,
8	,,	2·61	,,		3·77	3·88	,,
10	,,	13·1	188	[a]	3·00	3·20	3·37
7	,,	,,	,,	[a]	3·11	3·13	,,
55	,,	10·89	,,		3·34	3·36	,,
11	,,	13·1	94	[a]	2·12	2·07	2·32
13	,,	,,	37·6	[a]	1·41	1·29	1·23
56	,,	10·89	,,		1·39	1·46	,,
14	,,	13·1	15·1		1·08	0·97	0·57
59	,,	10·89	,,		1·46	1·36	,,
15	,,	13·1	7·5	[a]	0·824	0·815	0·30
60	,,	10·89	—		—	0·000	
65	$66{\cdot}0_5$	10·89	752		2·44	2·41	
57	,,	,,	188		0·908	0·91	
66	,,	,,	75·2		0·493	0·493	
58	,,	,,	37·6		0·366	0·368	
61	,,	,,	7·5		0·28	0·24	
62	,,	,,	—		—	0·000	
25	79·5	5·22	376		—	0·000	
17	,,	,,	188	[c]	2·6	—	
21	,,	,,	,,	[d]	2·45	2·6	
24	,,	,,	,,	[e]	2·68	—	
23	,,	2·61	,,	[e]	2·62	—	

[a] Runs in fractionated ethanol; other runs were in phthalate-dried ethanol, no significant difference being noted between the two sets. [b] Contained toluene-*p*-sulphonic acid (0·0019M); for other concentrations of acid see Fig. 1. [c] In ethanol containing 4% of water; the initial rate is given; however, the rate decreased rapidly to a very low value. The final solution from this run had an ultraviolet absorption curve closely resembling that of the oxopyrrole in acetic acid ($\lambda_{max.}$ 276, 347 mμ; log ε 4·25, 3·95); the decrease in rate is ascribed to production of acid by hydrolysis of the ethyl cyanoacetate. [d] Contained 0·2% (volume) of aqueous 0·024M-sodium hydroxide. [e] Contained 0·145M-triethylamine. [f] $1/R = 175 + 24/[CA]$, the equation derived from the line of Fig. 3.

For 2-α-cyano-α-ethoxycarbonylmethylene-5-oxo-3,4-diphenyl-3-pyrroline in ethanol, log $\varepsilon_{364} = 4{\cdot}313$. Figures for a typical run (No. 13, Table 1, where details of concentrations, etc., can be found) are:

Optical density	0·271	0·293	0·333	0·360	0·397	0·426	0·457	0·490	0·524	0·551
Time (min.)	0	10	20	30	40	50	60	70	80	90
10^3k_1 (min.$^{-1}$)	—	0·90	1·29	1·24	1·33	1·32	1·33	1·34	1·37	1·36

Although initial readings tended to be erratic, good first-order plots were obtained for most of the runs; however, average calculated k_1 values are appended, as variation of these from the graphical values is a measure of the precision of the results, probably ±5%.

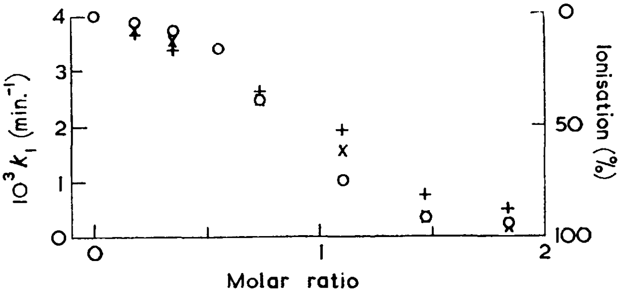


FIG. 1. *First-order rate coefficients for the reaction of ethyl cyanoacetate with 2-oxo-3,4-diphenyl-5-NNN′-trimethylguanidino-2H-pyrrole* (○) *in the presence of varying molecular amounts of toluene-p-sulphonic acid; and the degree of protonation of the pyrrole by the acid under comparable conditions, measured both at* 310 mμ (×) *and at* 370 mμ (+).

FIG. 2. *Reaction of ethyl cyanoacetate with sodium ethoxide* (□) *and with sodium ethoxide and 2-oxo-3,4-diphenyl-5-NNN′-trimethylguanidino-2H-pyrrole* (○) *under conditions summarised in Table* 2. (*Run nos. denoted on curves.*)

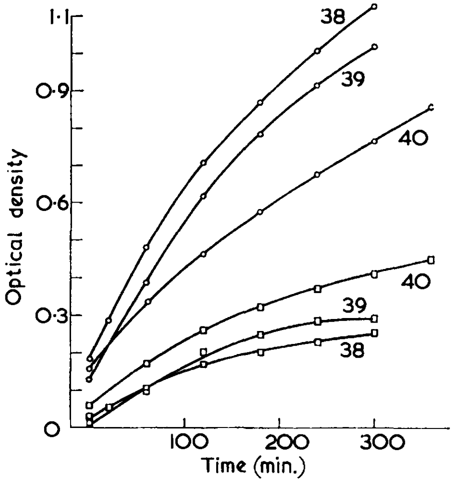
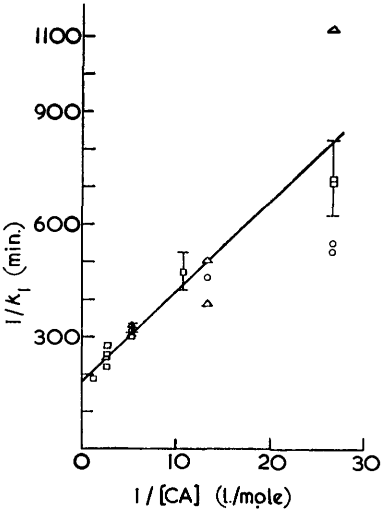


FIG. 3. *Reciprocals of the first-order rate coefficients for the reaction of ethyl cyanoacetate with 2-oxo-3,4-diphenyl-5-NNN′-trimethylguanidino-2H-pyrrole as a function of the reciprocal of the total concentration of the former in ethanol* (□), *in ethanolic* 0·00037M-*sodium ethoxide* (○) *and in* 0·0092M-*sodium ethoxide* (Δ) *at the b. p.*



Infinity run. A mixture of the oxopyrrole (5·00 ml. of $2{\cdot}61 \times 10^{-5}$M-solution), ethyl cyanoacetate (1 ml.) and ethanol was refluxed for 17 hr., cooled, and made up to 50·0 ml. with ethanol, and the optical density at 364 mμ was determined (Found: *D*, 0·537. Calc.: *D*, 0·537). The absorption of the solution in the range 310—420 mμ was within ±0·01 in log ε of that of a pure specimen of 2-α-cyano-α-ethoxycarbonylmethylene-5-oxo-3,4-diphenyl-3-pyrroline and showed only slight deviations outside this range.

Effect of sodium ethoxide. All these experiments were carried out with rigorously dried apparatus and with phthalate-dried ethanol. Preliminary runs with 0·0093M-sodium ethoxide gave rapidly increasing first-order coefficients, and the optical densities eventually exceeded the calculated infinity values. Thereafter the densities increased steadily and the solution obtained after several days was red and had a very high absorption at *ca.* 270 mμ; study of this reaction is in hand. Accordingly blank runs were carried out for each concentration of sodium ethoxide and for each concentration of ethyl cyanoacetate used, and the optical densities of runs with the oxopyrrole were corrected accordingly. Fig. 2 gives examples of optical density–time plots for the total and control runs. In spite of the large correction (as much as 50% as in run 40), good first-order plots were obtained as for run 47 (for concentrations, etc., see Table 2); corrections were greater for high ethoxide concentrations and for low ethyl cyanoacetate concentrations (pH-dependent) and were negligible for $<$0·0004M-sodium ethoxide provided that the concentration of the ethyl cyanoacetate exceeded 0·035M.

Details for run 47.

Optical density, reaction	0·164	0·312	0·449	0·579	0·708	0·798
Optical density, control	0·005	0·023	0·041	0·048	0·050	0·056
Optical density, corr.	0·159	0·289	0·408	0·531	0·658	0·742
Time (min.)	0	60	120	182	250	300
10^3k_1 (corr.; min.$^{-1}$)	—	1·08	1·06	1·08	1·10	1·09

Acid–Base Equilibrium Experiments.—Ionisation of 2-*oxo*-3,4-*diphenyl*-5-NNN′-*trimethylguanidino*-2H-*pyrrole in various concentrations of toluene*-p-*sulphonic acid.* Solutions to contain the oxopyrrole (5·44 × 10^{-5}M) and toluene-*p*-sulphonic acid were made up to 25·0 ml. with fractionated ethanol. Fractions of the oxopyrrole ionised for various molar ratios of the acid, determined at two wavelengths, are given in Fig. 1.

TABLE 2. *Corrected first-order rate coefficients* (*min.*$^{-1}$) *of the reaction between ethyl cyanoacetate* (CA), *and* 2-*oxo*-3,4-*diphenyl*-5-NNN′-*trimethylguanidino*-2H-*pyrrole* (OP) *in ethanol containing sodium ethoxide.*

Run	Temp.	10^5[OP]	10^3[CA]	10^4[NaOEt]	10^3k_1	R †
38	79·5°	5·44	376	92·6	4·15	4·18
39	,,	,,	188	,,	2·99	3·37
42	,,	10·89	,,	,,	3·28	,,
41	,,	5·44	75·2	,,	2·64 *	2·02
43	,,	10·89	,,	,,	1·99 *	,,
40	,,	5·44	37·6	,,	0·89	1·23
44	,,	,,	192	3·70	3·22	3·33
63	,,	10·89	75·2	,,	2·18	2·02
46	,,	,,	38·4	,,	1·90	1·25
45	,,	5·44	,,	,,	1·82	,,
54	,,	10·89	8·3	,,	1·52	0·33
51	,,	,,	3·8	,,	1·33	
48	,,	,,	2·3	,,	1·28	
47	,,	,,	0·75	,,	1·08	
64	,,	,,	0	,,	0·00	
52	66·0$_5$	,,	376	,,	1·56	
49	,,	,,	189	,,	0·86	
50	,,	,,	76·0	,,	0·58	
53	,,	,,	38·4	,,	0·426	

* Corrections by interpolation. † $1/R = 175 + 24/[\text{CA}]$.

Protonation of the oxo-pyrrole by ethyl cyanoacetate. Solutions containing (i) the oxopyrrole (5·44 × 10^{-5}M), (ii) the oxopyrrole (5·44 × 10^{-5}M) and ethyl cyanoacetate (0·377M), and (iii) the oxopyrrole (5·44 × 10^{-5}M) in an excess of ethanolic toluene-*p*-sulphonic acid (0·002M), were used. Results are tabulated:

	(i)	(ii)	(iii)
Optical density at 310 mμ	0·743	0·694	0·281
Optical density at 330·5 mμ (an isosbestic point)	0·232	0·233	0·233
Optical density at 370 mμ	0·078	0·100	0·264

The proportion of oxopyrrole protonated in solution (ii) is 11% (measurement at 310 mμ) or 12% (measurement at 370 mμ).

Acidity of ethyl cyanoacetate. A stock solution containing sodium ethoxide (1·85 × 10^{-2}M) and a convenient concentration of phenolphthalein was prepared. Aliquot parts (5·00 ml.)

were added to various amounts of ethyl cyanoacetate (CA) and made up to 10·0 ml. with ethanol, the optical densities being determined (1 cm. stoppered cells) at 564 mμ; these densities drifted slightly with time and were measured after *ca.* 5 min. The ratio $D_{\text{sol.}}/D_{[\text{CA}]=0} = f$ is given below. It is apparent that the ethoxide concentration cannot be ignored. Nevertheless the ratio

10^3[CA] ...	377	151	75·5	37·7	30·2	22·6	15·1	11·3	9·4	7·6	7·2	6·8	6·4
f	0·027	0·096	0·226	0·426	0·522	0·653	0·786	0·863	0·92$_3$	0·97$_4$	0·97$_4$	0·99$_6$	0·99$_6$
r	1·1	1·6	2·1	2·1	2·5	2·7	2·3	1·4	—	—	—	—	—

$$r = K_{\text{ind.}}/K_{\text{CA}} = f([\text{CA}] - [\text{NaOEt}])/(1 - f) \,.\, [\text{NaOEt}]$$

is given; thus the acid dissociation constant $K_{\text{ind.}}$ of phenolphthalein in ethanol is approximately twice that of ethyl cyanoacetate (K_{CA}).

DISCUSSION

The mechanism proposed by Patai *et al.*[4] for the condensation of active methylene compounds with aldehydes—namely, either a rate-determining ionisation for malononitrile (in water) or a rate-determining second-order reaction of the enolate of ethyl cyanoacetate, diethyl malonate, or malononitrile in ethanol with the aldehyde—may account for their observations (but see below) but is inapplicable to our results. In the present instance the order in ethyl cyanoacetate is non-integral and decreases with increasing cyanoacetate concentration. First-order kinetics affected to a smaller extent in this way by subsequent steps have been discussed;[5] however an alternative explanation—a pre-equilibrium condensation step, with the concentration of the intermediate appreciable and a later rate-determining reaction—is considered a more reasonable explanation in this case.

The virtual independence of the rate (except at very low ethyl cyanoacetate concentrations) of added base excludes a rate-determining base-catalysed ionisation or bimolecular elimination step, whereas the near-stoicheiometric inhibition of the reaction by acid, which parallels the spectroscopically determined ionisation of the oxopyrrole (Fig. 1; determined for toluene-*p*-sulphonic acid under conditions closely comparable with those in the kinetic runs), indicates that the reactive molecular species is of the same net-charge type as that of the oxopyrrole. The mechanism proposed in scheme (*a*) on chemical grounds is thus qualitatively supported and the rate-determining step identified (probably) as the elimination step (c) ⟶ (d), the alternative[6] [isomerisation (b) ⟶ (c)] being expected to be fast as for the ionisation of ethyl cyanoacetate. It being of interest to establish that such a scheme is in quantitative accord with the results, the following simplified analysis for runs in the presence of significant concentration of sodium ethoxide was undertaken in which hydrolysis (ethanolysis; in the ionic sense) of ethyl sodiocyanoacetate is neglected. The concentration of the ethyl cyanoacetate anion is taken equal to that of the sodium ion. The activity coefficients (which however may be as high as 400 for charged species in ethanol[7]) are neglected; the ethyl cyanoacetate concentration being usually more than 100 times that of the oxopyrrole, the following equations then apply:

$$[\text{NaOEt}]_{\text{added}} = [\text{CA}^-]$$

$$[\text{CA}] = [\text{CA}]_{\text{added}} - [\text{NaOEt}]_{\text{added}}$$

We write [OP] and [OPH$^+$] for the actual concentrations of the oxopyrrole and its

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[4] Patai and Israeli, *J.*, 1960, (*a*) 2020, (*b*) 2025; (*c*) Patai and Zabicky, *J.*, 1960, 2030; (*d*) Patai Zabicky, and Israeli, *J.*, 1960, 2038.

[5] (*a*) Bird, Hughes, and Ingold, *J.*, 1954, 634; (*b*) Bunton, Greenstreet, Hughes, and Ingold, *J.*, 1954, 647.

[6] Noyce, Pryor, and Bottini, *J. Amer. Chem. Soc.*, 1955, **77**, 1402; Noyce and Reed, *ibid.*, 1958. **80**, 5539.

[7] Bates, " Electrometric pH Determinations," Wiley, New York, 1954, p. 136.

protonated form, respectively; [PCA] = the concentration of the intermediate [I; X = (b); R = Me, R′ = Me]; [G] = the concentration of the guanidinium enol ion [I; X = (c); R = Me, R′ = Me]; $[G^-]$ that of its anion $(G - H^+)$; p = total concentration of all forms of the oxopyrrole added initially, or not converted into the product [II; X = (d)] at subsequent times.

Equilibrium constants are defined as follows:

$$\begin{aligned}
[CA^-][H^+] &= K_{CA}[CA] \\
[CA][OP] &= K_1[PCA] = K_1K_2[G] \\
[OP][H^+] &= K_B[OPH^+] \\
[G^-][H^+] &= K_{A,G}[G] \\
[G][H^+] &= K_{B,G}[GH^+]
\end{aligned}$$

Furthermore

$$[OP] + [OPH^+] + [PCA] + [G] + [G^-] + [GH^+] = p.$$

These equations lead to:

$$[OP]\{1 + K_{CA}[CA]/K_B[CA^-] + [CA](1 + K_2 + K_{A,G}[CA^-]/K_{CA}[CA] + K_{CA}[CA]/[CA^-]K_{B,G})/K_1K_2\} = p: \qquad (1)$$

whence, if $dp/dt = -k_1[G]$,

$$\text{then } -p\ dt/dp = \{K_1K_2 + K_{A,G}[CA^-]/K_{CA}\}/[CA]k_1 + (1 + K_2)/k_1 + K_1K_2K_{CA}/k_1K_B[CA^-] + [CA]K_{CA}/[CA^-]K_{B,G}k_1. \qquad (2)$$

Provided that $[GH^+]$ is negligible in the absence of added acid, a plot of reciprocal rate against 1/[CA] would yield an intercept due to the second and third terms of equation (2) and a slope due to the first bracket; both slope and intercept would vary with sodium ethoxide concentration should the concentration $[G^-]$ and $[OPH^+]$ be significantly high.

On the other hand, should the concentration of the ionic species $[OPH^+]$, $[G^-]$, and $[GH^+]$ all be low compared with p, the equation reduces to:

$$-p\ dt/dp = K_1K_2/[CA]k_1 + (1 + K_2)/k_1, \qquad (3)$$

which would be applicable equally to neutral solutions (where the protonation of ethyl cyanoacetate by the oxopyrrole is not more than 12% under the experimental conditions) as well as to the alkaline solutions.

In fact, a plot of the reciprocals of the observed rates for both neutral and alkaline solutions against 1/[CA] (Fig. 3) tends to the same straight line at the higher concentrations of ethyl cyanoacetate. (In Fig. 3 [CA] refers to the total added concentration of the ethyl cyanoacetate; ionisation of the latter would, at the most, displace some points by a small amount; in Fig. 4 a correction for this ionisation has been made.) The scatter of points from the line is magnified by the reciprocal plot (in Fig. 3 the effect of a possible error of $\pm 0{\cdot}2 \times 10^{-3}$ min.$^{-1}$ in the rates is shown by vertical lines for points in neutral ethanol), and is greater than any systematic deviations at [CA] > 0·05M. At lower [CA], however, systematic deviations are manifest for both neutral and alkaline solutions and, as can be seen from the plot of reciprocal rate against cyanoacetate concentration plot (Fig. 4), their magnitude is base-dependent. Being in the direction of increased rates, these deviations cannot be accounted for by use of equation (2); however a slow side-reaction of zero order in [CA] but influenced by the pH would perhaps explain this trend. Nevertheless, that scheme (a) and equation (3) tend to predict the influence of ethyl cyanoacetate concentration upon the rate, at high concentration, is supported by the last column of Tables 1 and 2; however, these predictions are useless at [CA] < 0·05M (at which concentrations the stoicheiometry has not been established). The more precise runs at 66° fit an equation of the same form, *viz.*, $1/\text{Rate} = 115 + 250/[\text{CA}]$, if an arbitrary (and experimentally unsupported) reduction of $0{\cdot}2 \times 10^{-3}$ min.$^{-1}$ is applied to the observed rates (all runs at this temperature were done at the same concentration of the oxopyrrole):

Run	65	57	66	58	61	52	49	50	53
10^3 [(obs. rate) $-$ 0·2]	2·24	0·708	0·293	0·166	0·08	1·36	0·66	0·38	0·226
$10^3/(115 + 250/[\text{CA}])$	2·23	0·69	0·29	0·15	0·03	1·28	0·70	0·30	0·15

It should be noted that the alternative scheme of two steps at comparable rates[5] leads to a rate expression of similar form (for the aldol condensation of acetaldehyde,[8] $-3\mathrm{d}t/\mathrm{d}a = 1/ak_1 + k_{-1}/a^2k_1k_2$) to that of equation (3). However, in the present instance scheme (b),

$$\text{Oxopyrrole} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \text{Intermediate} \xrightarrow{\text{CN}\cdot\text{CH}_2\cdot\text{CO}_2\text{Et}} \text{Products}$$

Scheme (b)

which seems *a priori* unlikely, would be required to explain the kinetic form observed at the higher ethyl cyanoacetate concentrations. A scheme based on a partly rate-determining ionisation of ethyl cyanoacetate would not only fail to account for the observed kinetics, but would also require that the rate of ionisation be comparable (within a factor of not more than ~5) with the observed rate; however, ethyl cyanoacetate * enolises at 25° in neutral water at a rate[9] $k_1 = 7 \times 10^{-2}$ min.$^{-1}$, with an activation energy of 17 kcal. mole^{-1}.

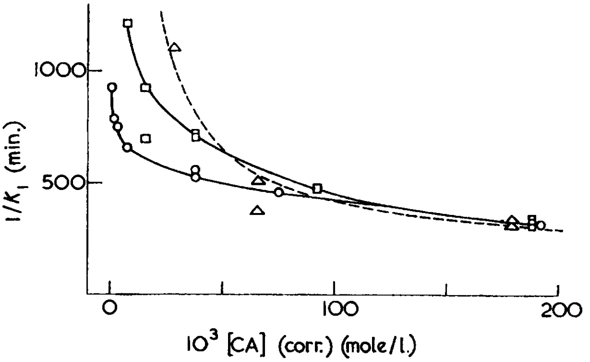

FIG. 4. *Reciprocals of the first-order rate coefficients for the reaction of ethyl cyanoacetate with* 2-*oxo*-3,4-*diphenyl*-5-NNN′-*trimethylguanidino*-2H-*pyrrole as a function of the total concentration of the former in low concentration; points are marked as in Fig.* 3.

[CA] *refers to the concentration of ethyl cyanoacetate corrected by subtraction of the concentration of sodium ethoxide. The broken curve corresponds to the line of Fig.* 3 ($1/\text{Rate} = 175 + 24/[\text{CA}]$).

Although equation (2) would hold for reactions in the presence of strong acid, it cannot be simply applied. Initial rates, however, are given by equation (3) when the term p is replaced by (p *minus* the concentration of added acid) (absence of hydrolysis of the acid-oxopyrrole salt being assumed); as the reaction proceeds, the guanidine so produced would tend to become protonated in proportion to its concentration and basic strength relative to those of the remaining oxopyrrole; thus an increase in specific rate during a run might be expected. Although several such runs did show deviations towards higher rates, these were not sufficiently greater than the experimental error to be significant. That the term p of equation (3) should be reduced by the amount of the protonated, and hence unavailable, oxopyrrole, is indicated when the product of the rate in neutral solution

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* In ref. 4*d* the dissociation constant for diethyl malonate is misquoted (from ref. 9) as $K_a = 5 \times 10^{-4}$ (ref. 9 gives 5×10^{-14}), as is the constant for ethyl cyanoacetate as 10^{-9} (ref. 9 gives $<10^{-9}$; an empirical correlation graph given[9] does lead to 10^{-9}; the authors[9] state, however, that their graph is very rough, and is given only as a basis for argument and not for prediction—in fact, the graph leads to values of 10^{-7} for malononitrile and 10^{-10} for diethyl malonate, values quite at variance with measured values), and thus the argument on p. 2042 of ref. 4*d* is unfounded.

[8] Bell and McTigue, *J.*, 1960, 2983.

[9] Pearson and Dillon, *J. Amer. Chem. Soc.*, 1953, **75**, 2439.

and the fraction of the oxopyrrole not protonated in the acidic solution (Z; *viz.*, the predicted initial rate) is compared with the observed rate † for the latter solution:

10^5 [Acid]	0·75	1·51	3·01	4·52	6·02	7·54
$10^3 k_1$ (obs.)	3·9	3·7	2·5	1·0	0·4	0·2
Z	3·7	3·5	2·5	1·8	0·5	0·3

The elimination of the guanidine residue in the above reactions is apparently a novel aspect of guanidine chemistry (although the hydrolysis of the guanidinopyrroles [2] can be regarded as a trivial example). However, two other examples of reactions, including an elimination, of a guanidine residue in which this behaves as a " pseudo-halogen " have been observed and are under investigation in this laboratory.[10]

Comments on the Mechanism Proposed by Patai, Israeli, and Zabricky.—In a series of papers [4] Patai *et al.* propose a mechanism for the condensation of ethyl cyanoacetate, cyanoacetamide, malononitrile, and diethyl malonate with a number of aldehydes, based upon the general scheme:

$$\mathrm{RR'CH_2} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{RR'CH^-} + \mathrm{H^+} \quad . \; . \; . \; . \; . \; . \; . \; . \; . \; . \quad (3)$$

$$\mathrm{RR'CH^-} + \mathrm{R''R'''CO} \xrightarrow{k_3} \mathrm{RR'CH{\cdot}CR''R'''{\cdot}O^-} \quad . \; . \; . \; . \; . \; . \; . \; . \; . \quad (4)$$

Scheme (c)

step (4) is followed by fast steps. They commented " If in this sequence the dissociation rate k_1 is very slow compared with other rates, the result will be overall of the first order, *i.e.*, of the first order in $\mathrm{RR'CH_2}$ and of zero order in the other reactants; " and they concluded "The experiments described above show that the reaction between malonitrile [*sic*] and aromatic aldehydes in water is governed by a rate-determining unimolecular ionisation of the malononitrile molecule. . . ." They comment on the difference in rates dependent on the aldehydes used, but they accept the explanation of Bird, Hughes, and Ingold [5] as adequate in this instance, and they have difficulty in explaining the faster rates, of strictly second order, in ethanol for this reaction.[4b] Yet the first-order rates for the condensation of malonitrile with aldehydes in water at 35° and apparently at pH 7 were given as *ca.* 6×10^{-5} sec.$^{-1}$ for *p*-anisaldehyde; between 12·4 and $20{\cdot}7 \times 10^{-5}$ sec.$^{-1}$ for benzaldehyde, depending on the concentration (they postulate abnormal behaviour for benzaldehyde to explain similar behaviour in its condensation with ethyl cyanoacetate in water [4c]); between 19·5 and $25{\cdot}5 \times 10^{-5}$ sec.$^{-1}$ for *p*-chlorobenzaldehyde; and between 47 and $55{\cdot}5 \times 10^{-5}$ sec.$^{-1}$ for *p*-nitrobenzaldehyde; with activation energies for these reactions which vary by a factor of four: 9300 ± 300 cal. mole^{-1} for *p*-anisaldehyde; 7200 ± 200 for benzaldehyde; and 2400 ± 300 for *p*-nitrobenzaldehyde.

For scheme (c) it can be shown, with the usual assumptions that:

$$\mathrm{Rate}^{-1} = [\mathrm{H^+}]k_{-1}/k_3k_1[\mathrm{RR'CH_2}][\mathrm{R''R'''CO}] + 1/k_1[\mathrm{RR'CH_2}] \qquad (5)$$

(equivalent to Bird, Hughes, and Ingold's equation [5a]). If we assume that for the reaction between malononitrile and *p*-nitrobenzaldehyde the first term is negligible, then $k_1 = 55{\cdot}5 \times 10^{-5}$ sec.$^{-1}$. Then for the reaction with anisaldehyde the reciprocal of the first term will be $0{\cdot}149 \times 10^5$ and that of the second term $0{\cdot}018 \times 10^5$; with this weight the reaction would be within *ca.* 10% of second order, which was not observed. Further, the plot of the reciprocal rates for the reaction of malononitrile with benzaldehyde in water against the reciprocal of the aldehyde concentration (rates taken from ref. 4*a*) gives a plot curved downwards and hence equation (5) is not obeyed. In any case the rates and energies of activation for the ionisation of malononitrile in water are known; [9] in neutral solution at 25° in water the initial first-order rate coefficient for this reaction is 9×10^{-1} min.$^{-1}$ and slightly less in dilute acid; its activation energy is 18 kcal. mole^{-1}. It is thus

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† Added at the suggestion of a referee.

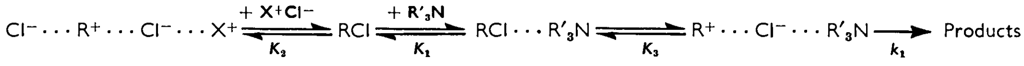
[10] Banfield and McGuinness, unpublished work.

abundantly clear that the explanations of Patai *et al.* are inadequate, the second term in equation (5) (less than 67 sec.) being small compared with the smallest reciprocal rate (1800 sec.) and negligible compared with that for *p*-anisaldehyde (14,900 sec.).

When applying a scheme analogous to (a) and equation (2) to this reaction, it is qualitatively possible to avoid the difficulties mentioned above, and to account for the maximum in rates at *ca.* 30% ethanol in water (and of explaining similar phenomena observed for other reactions of this type [4c,d]). For a large excess of aldehyde, and on the basis of a rate-determining elimination from a species of type (G$^-$), the right-hand side of equation (2) would be altered by a factor of $[\text{CA}^-]K_{\text{A, G}}/[\text{CA}]K_{\text{CA}}$; however, figures given by Patai *et al.*[4a] for comparable concentrations of malononitrile and benzaldehyde (the former never being in substantial excess) are not in quantitative agreement with the appropriately modified version of equation (5); in fact the rates are reasonably described by an equation of type: $10^5k_1 = 12{\cdot}3 + a[\text{BA}]$ sec.$^{-1}$, where [BA] = the concentration of benzaldehyde; thus, on the available evidence, scheme (a) does not describe the kinetics of this reaction.

An Alternative Interpretation of Some Results of Ingold's School.[5]—These authors observed first-order rates, for a presumably unimolecular ionisation of *m*-chlorobenzhydryl chloride, which varied both with the nature of the subsequent reaction steps and with the concentration of the reagent reacting with the carbonium ion; these rates did not extrapolate to the same point at zero concentration of reagent as required by the simple theory. Their discussion of this point centred on border-line mechanisms with varying participation of the reagent. While reasonable as a qualitative explanation, this theory is unsatisfactory from a quantitative point of view (it has been criticised on theoretical grounds [11]) and, as subsequent workers have used superficially parallel behaviour to invoke the same explanation in other cases, a quantitative interpretation of these facts seems desirable.

Well-authenticated examples of this type of behaviour seem limited to ionisation in solvents of relatively low dissociating power (*e.g.*, sulphur dioxide, benzene [11,12]) in cases where the same components react in water in a conventional S_N1 manner. In the former type of solvent it might be expected that polar molecules or ion-pairs would tend to be solvated by polar molecules in preference to solvent molecules. A scheme of form (d) leads to the rate equation, when R is the total concentration of halide present up to the rate-determining step:



$$\text{Cl}^-\cdots\text{R}^+\cdots\text{Cl}^-\cdots\text{X}^+ \underset{K_2}{\overset{+\,\text{X}^+\text{Cl}^-}{\rightleftharpoons}} \text{RCl} \underset{K_1}{\overset{+\,\text{R}'_3\text{N}}{\rightleftharpoons}} \text{RCl}\cdots\text{R}'_3\text{N} \underset{K_3}{\rightleftharpoons} \text{R}^+\cdots\text{Cl}^-\cdots\text{R}'_3\text{N} \xrightarrow[k_1]{} \text{Products}$$

Scheme (d)

$$-R\,\mathrm{d}t/\mathrm{d}R = (1 + K_3)/k_1 + K_1K_3/k_1[\text{Amine}] + K_1K_3[\text{X}^+\text{Cl}^-]/k_1K_2[\text{Amine}] \qquad (6)$$

(where k_1 is dependent on nature of the amine); this explains qualitatively the above results and explains at least as well quantitatively the variation of the rate with amine concentration as do the linear extrapolations; [5] this may be seen from the reciprocal rate–reciprocal amine concentration plot (Fig. 5), while it retains the form of Bird, Hughes, and Ingold's equation for the effect of chloride ions on the rate. (In Fig. 5 rates are taken from ref. 5*a* for reactions of *m*-chlorobenzhydryl chloride with pyridine and triethylamine, and from ref. 5*b* for the reaction of t-butyl bromide with pyridine.) In scheme (d) the form of the complexes is not of kinetic consequence; for example, the ion quadrupole ($\text{Cl}^-\cdots\text{R}^+\cdots\text{Cl}^-\cdots\text{X}^+$) might equally be replaced by a solvated ion pair of type ($\text{X}^+\text{Cl}^-\cdots\text{RCl}$); nor is the location of the rate-determining step necessarily as shown [an alternative is the step between the complex ($\text{RCl}\cdots\text{R}^-{}_3\text{N}$) and the quadrupole; constants would be changed in the above equation, but not its form]. Thus scheme (d) seems a

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[11] Gold, *J.*, 1956, 4633.

[12] Hughes, Ingold, Mok, Patai, and Pocker, *J.*, 1957, 1265.

reasonable alternative to that invoked by Ingold and his co-workers [12] to explain similar phenomena in benzene,[13] which required at least two rate-determining steps of comparable magnitude (an event which, being fortuitous, might be expected to be uncommon) in a scheme depending on competitive reactions and rearrangement of ion quadrupoles. Our scheme is fundamentally similar and it rests on similar arguments and concepts to those of Ingold's school, but it differs in that one rate-determining step is replaced by a mass-significant pre-equilibrium.

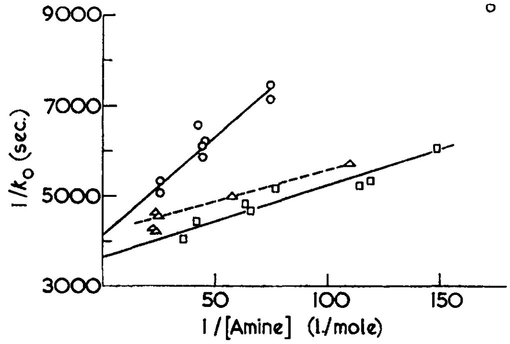

FIG. 5. *Reciprocals of the specific initial rates of the reactions of* m-*chlorobenzhydryl chloride with pyridine* (○) *and with triethylamine* (□) *and of the reaction of t-butyl bromide with pyridine* (△) *as a function of the reciprocal of the concentration of the amine, calculated from values given in the literature.*[5]

However, whichever explanation proves appropriate for reactions in sulphur dioxide, it is clear that phenomena of this type—S_N1 reactions of a rate depending on the nature and/or concentration of the product-determining reagent—are to be expected only in solvents of low dielectric constant; hence care should be exercised in the parallel explanation of superficially similar behaviour, especially where the complexity of the reaction renders other explanations possible and where the phenomena are observed in aqueous solution.

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[13] Hughes, Ingold, Patai, and Pocker, *J.*, 1957, 1206, 1230, 1256; Hughes, Ingold, Mok, Patai, and Pocker, *J.*, 1957, 1220; Hughes, Ingold, Mok, and Pocker, *J.*, 1957, 1238.