Mechanisms of Heterocycle Ring Formation. Part 5.[1] A Carbon-13 Nuclear Magnetic Resonance Study of Pyrazolinone Synthesis by the Reaction of β-Ketoesters with Substituted Hydrazines

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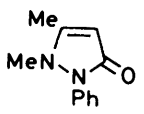
The 16 reactions between each of four hydrazines and four β-ketoesters have been followed by ^{13}C n.m.r. spectroscopy. Peaks were assigned to starting materials, intermediates, and products, and reaction mechanisms determined and rationalized. Most reactions proceed by attack of the least hindered hydrazine nitrogen atom on the keto carbon group of the ketoester. Relative rates of nucleophilic attack determine the build-up of intermediate and in some cases the nature of the products formed.

The pyrazolin-5-one nucleus has occupied an important place in medicinal and dye chemistry for a century,[2a,b] Knorr[3] having prepared antipyrine (**1**)[2a] in 1884 and Ziegler[4] obtaining the dye tartrazine (**2**)[2b] in 1888. Knorr's original use of ethyl acetoacetate and phenylhydrazine,[5] *i.e.* condensation of a β-ketoester with hydrazine or its derivatives, remains the standard method[2b,6,7] of pyrazolin-5-one synthesis.

Although the isolation of the crystalline phenylhydrazone of ethyl acetoacetate (Scheme 1) (**9b**; R^3 = Et) and its subsequent



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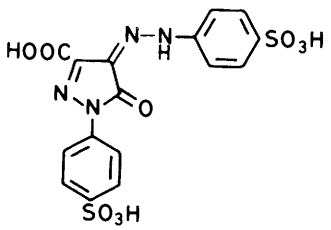


(**2**)

thermal conversion into 1-phenyl-3-methyl-2-pyrazolin-5-one (**14b**) was reported in 1891,[8] our knowledge of the mechanism of this reaction was, until recently, fragmentary. Qualitative differences in ease of ring closure were reasonably ascribed[9,10] to favourable–unfavourable (*syn versus anti*) stereochemistry about the hydrazone carbon–nitrogen double bond.

Recently, the individual steps, including relative rates, in the reaction between hydrazine and ethyl acetoacetate were outlined[11] on the basis of a ^1H n.m.r. study in aqueous solution. Our own interest in this mechanism arose from our previous studies[12,13] of examples of heterocyclic ring formation and was prompted by two inter-related questions. (i) Will the reversal in isoxazolinone isomer ratios observed[14] when ethyl acetoacetate and ethyl α-methylacetoacetate react with hydroxylamine carry over into the pyrazolinones? (ii) What will be the regiochemical outcome when methylhydrazine, phenylhydrazine, and 1-methyl-2-phenylhydrazine are used?

Accordingly, we have probed for intermediates on the reaction pathways leading from hydrazines (**3**) and (**17**) and β-ketoesters (**4**) to the product pyrazolinones (**14**)—(**16**) (Scheme 1) and (**27**) and (**28**) (Scheme 2), respectively, by ^{13}C n.m.r. spectroscopy.

Results and Discussion

Reactants were mixed in a 1:1 mole ratio in CD_3CN solution, and the spectrum monitored for the disappearance of starting material peaks, for the initial formation, maximum concentration, and decay of intermediate(s), and for the appearance of product. Spectra correlations for starting materials and products were based upon authentic spectra determined in the present work and/or available in the literature. Peaks associated with intermediates were assigned by analogy to published data for similar compounds.

C-13 *Assignments and Characterization of Intermediates.*—Literature ^{13}C n.m.r. shifts for monosubstituted hydrazines (**3**)[15a,b] and β-ketoesters (**4**)[15c–f,16] agree quite closely with the assigned values assembled in Tables 1 and 2, respectively. The upfield shifts of the methyls in compounds (**17**) relative to methylhydrazine (**3a**) are attributable to γ-substituent effects.[17]

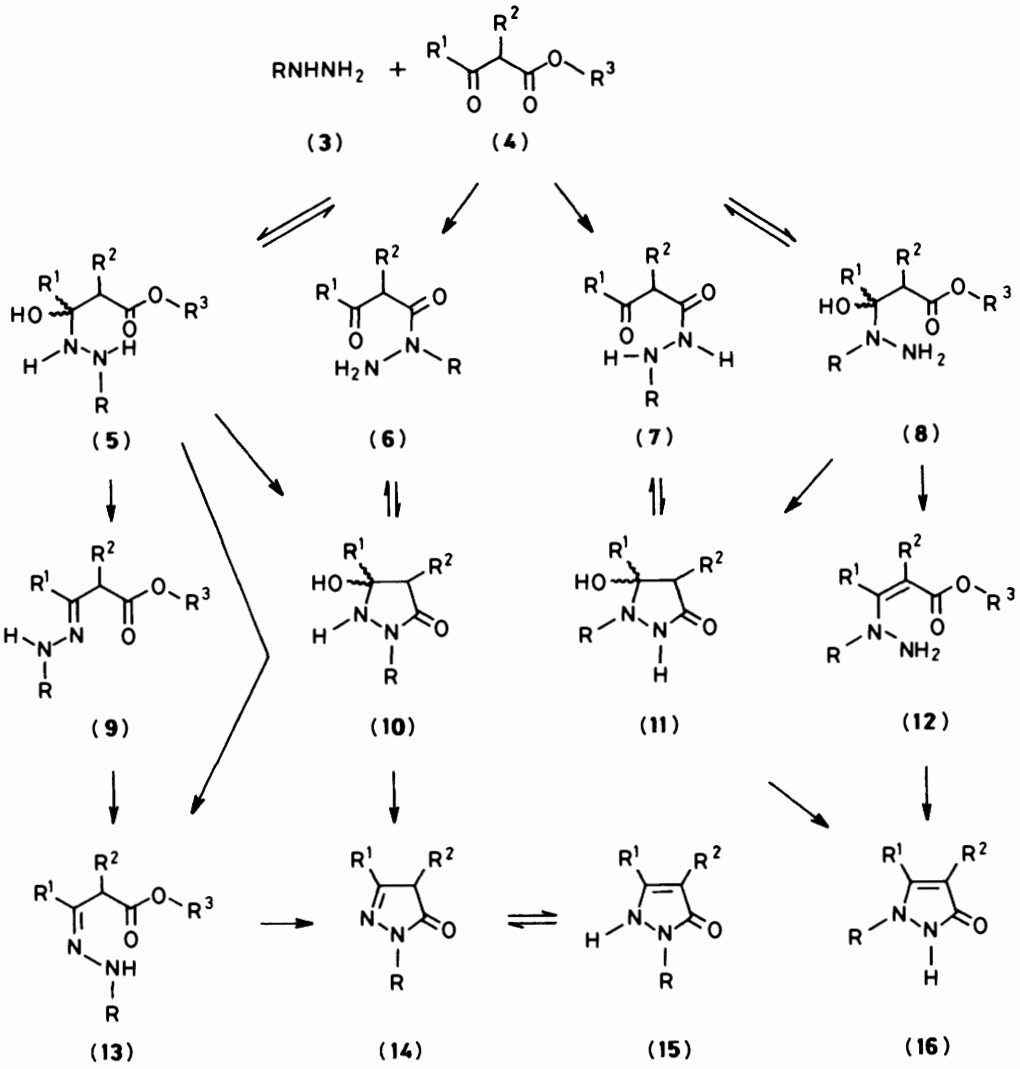
Peak positions for products (**14**)—(**16**) are given in Table 3 and those for products (**27**) and (**28**) in Table 4. Although many simple pyrazolinones have been prepared (>200 are described in a 1958 review[2a]), the range of published[18–21] ^{13}C values and assignments for these compounds seems to be quite restricted.

Comparison of chemical shifts of 2-pyrazolin-5-ones (**14**) (Table 3) with those for 3-pyrazolin-5-ones (**15**) and (**27**) (Tables 3 and 4) reveals significant differences. Whereas C-4 resonates within the range δ 83.5—109 p.p.m. (sp^2 carbon) in the ring system of (**15**) and (**27**), it appears close to δ 40 p.p.m. in the spectra of compounds (**14b** and **f**), confirming its sp^3 character here. Turning to C-5, we find a consistent regularity not only in the individual shifts of compounds (**27**) (cross-conjugated carbonyl), each being found in the range δ 166.0—167.4 p.p.m.,† but also in those of compounds (**14**) where the range is δ 172.2—172.3 p.p.m.‡ In the NH series (**15a**—**h**), C-5 resonates at higher fields, the values reflecting the great importance of canonical form (**30**) in the NH derivatives where strong H-bonding is possible.

Randall *et al.*[18] have calculated the chemical shift of C-5 in 1-phenyl-3-methyl-5-hydroxypyrazole to be δ 145.8 p.p.m. Under most conditions the 5-hydroxypyrazole tautomer is only a minor contributor to the tautomeric equilibrium.[22] However, the zwitterionic canonical form (**30**) is important and is probably responsible for the smaller chemical shifts observed for C-4 in (**15e** and **f**) [compared with (**15a** and **b**)]. Only minor changes are observed between (**15c** and **g**) and between (**15d** and **h**). There is no useful trend in the chemical shifts recorded for C-3: the spread in our values is consonant with those reported in the

† Begtrup[20] reports a value of δ 165.7 for (**15b**) and 165.9 p.p.m. for 2-methyl-1-phenyl-3-pyrazolin-5-one.

‡ We suggest that δ 167 and 172 p.p.m. be regarded provisionally as reference values for the carbonyl carbons in fixed 3-pyrazolin-5-ones and 2-pyrazolin-5-ones, respectively.



	a	b	c	d	e	f	g	h
R	Me	Ph	Me	Ph	Me	Ph	Me	Ph
R^1	Me	Me	Me	Me	Ph	Ph	Ph	Ph
R^2	H	H	Me	Me	H	H	Me	Me
R^3	Me	Me	Et	Et	Et	Et	Et	Et

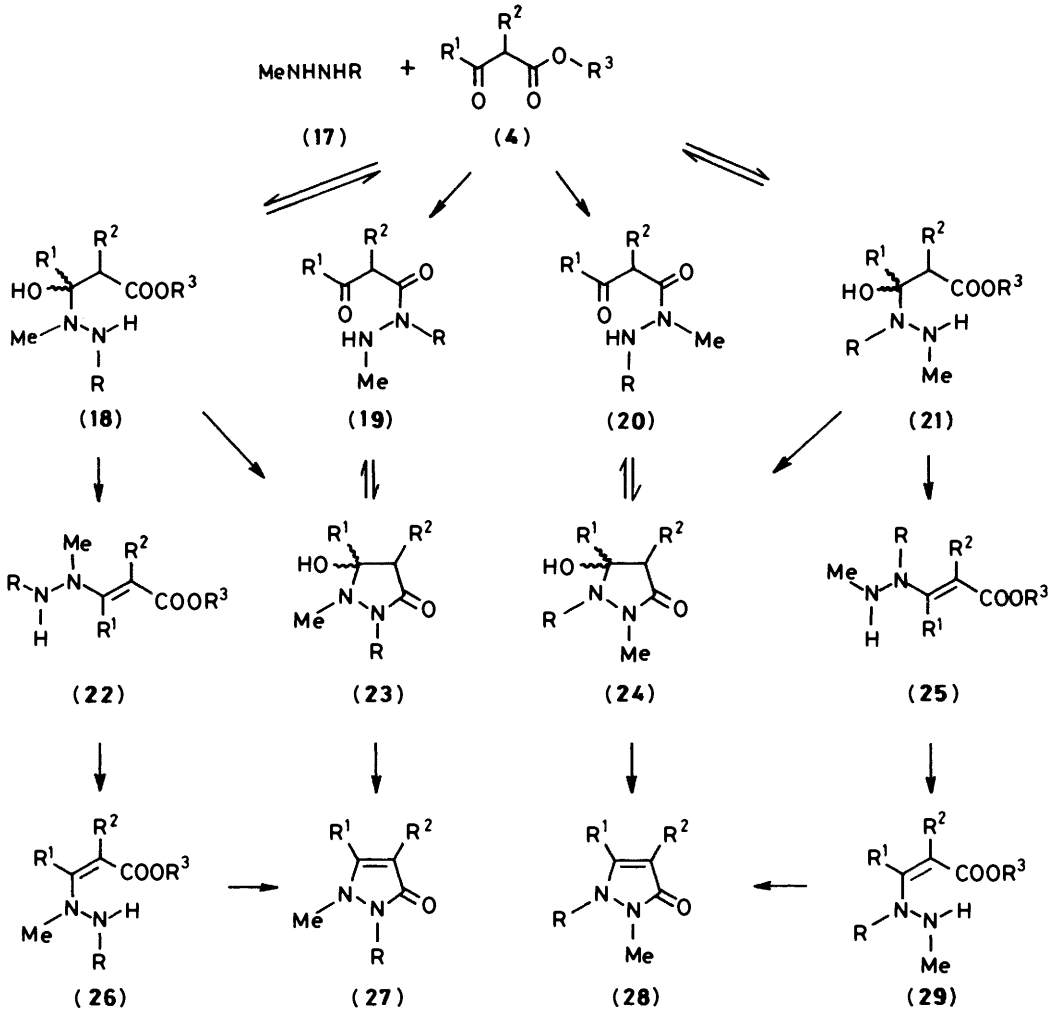
Scheme 1. Mechanism of the reaction of methylhydrazine and phenylhydrazine with β-ketoesters

literature for comparable enaminones (δ 145—160 p.p.m.)[23] and phenylhydrazone (δ 145—150 p.p.m.).[24]

Table 5 gives pertinent information regarding intermediates (**9**) and (**13**), identified spectroscopically in the reaction of β-ketoesters (**4**) with methyl- and phenyl-hydrazine. No essential change in the peak position(s) for the ester alkyl carbons (R^3) accompanies hydrazone formation, although there is a slight downfield shift for the ester carbonyl C-3. Further comparison of values in Table 5 with those of appropriate keto forms in Table 2 documents a shielding of R^1(Me) and C-2 in (**9**) and (**13**), its size being directly influenced by steric effects involving the carbon nitrogen double bond. Those carbon atoms which are *syn* to NHR, as in the case of methyl (R^1) in (**9b—d**) or C-2 in (**13b—f**), are shifted to even higher field than those *anti* to NHR. As expected, a considerable diamagnetic shift, *ca.* 50—60 p.p.m., is observed in the signal position of C-1 when C=O becomes C=NNHR.

During the course of the reaction of (**3**) and (**4**) there was no available spectral peak which could reasonably be assigned to C-3 of the intermediate 3-hydroxy-5-pyrazolidinone (**10**) (Scheme 1). When R^1 = Me [(**4a** and **c**)], the signal for C-3 in (**10a—d**) should have appeared close to the range δ 85.7—86.9 p.p.m. reported earlier[25] for the heterosubstituted carbon in three simple aliphatic ketone–hydrazine adducts, $MeRC(OH)NHNH_2$ [*cf.* structure (**31**)]. When R^1 = Ph (**4e** and **g**), the expected range for C-3 in (**10e—h**) is calculated to be δ 93.2—94.4 p.p.m. (*cf.* CH_2 shifts of δ 57.0 in EtOH and 64.5 p.p.m. in $PhCH_2OH$,[17] respectively).

Table 6 gives chemical shifts and assignments of intermediate (**22a**), seen in the reaction of 1,2-dimethylhydrazine (**17a**) with



	a	b	c	d	e	f	g	h
R	Me	Ph	Me	Ph	Me	Ph	Me	Ph
R^1	Me	Me	Me	Me	Ph	Ph	Ph	Ph
R^2	H	H	Me	Me	H	H	Me	Me
R^3	Me	Me	Et	Et	Et	Et	Et	Et

Scheme 2. Mechanism of the reaction of 1,2-dimethylhydrazine and 1-methyl-2-phenylhydrazine with β-ketoesters

Table 1. Carbon-13 chemical shifts (p.p.m.) of substituted hydrazines (**3a** and **b**) and (**17a** and **b**) (Schemes 1 and 2)[a]

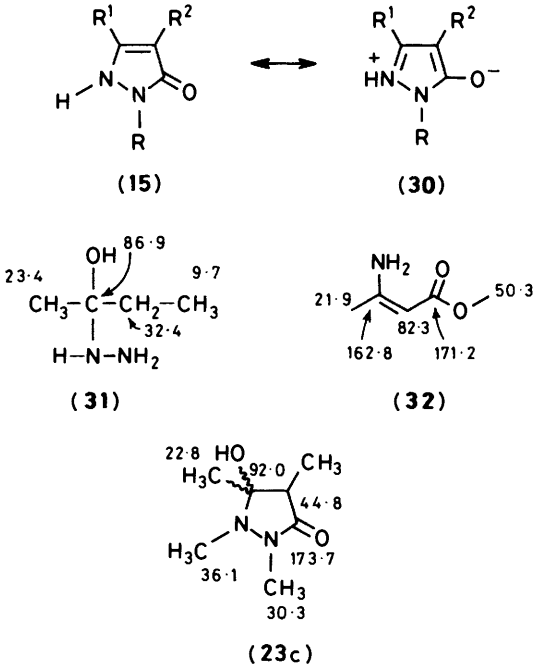
No.	Me	C-1[b]	C-2	C-3	C-4	Ref.
(**3a**)	43.1					15*a*
(**3b**)		153.0	113.1	129.9	119.3	15*b*
(**17a**)	37.8					
(**17b**)	39.1	150.7	113.9	130.1	119.5	

[a] Shifts are relative to CD_3CN at 1.3 p.p.m. [b] *ipso* carbon, with remaining ring carbons numbered in order.

methyl acetoacetate (**4a**), and intermediates (**22b** and **f**) seen in the reactions of 1-methyl-2-phenylhydrazine (**17b**) with (**4a**) and ethyl α-methylacetoacetate (**4c**), respectively (Scheme 2). There is a strong correlation between these results and the values recorded[26] for methyl (*Z*)-3-aminobut-2-enoate (**32**); the only significant effect of replacing NH_2 [in (**32**)] by NMeNHR [in (**22a** and **b**)] is an upfield shift of *ca.* 7 p.p.m. in the signal position of allylic methyl R^1. We assign the *E*-stereochemistry to (**22**); its conversion into product (**27**) must proceed *via* the (*Z*)-diastereoisomer (**26**).

The transient intermediate (**23c**) was identified (see Scheme 3) at low concentration in the reaction of ethyl α-methylacetoacetate (**4c**) and 1,2-dimethylhydrazine (**17a**). Given the tabular values of incremental substituent effects[17] for NH_2, NHR, and $CONH_2$, plus literature assignments for the *gem*-hydrazinohydroxy adduct (**31**),[27] estimated chemical shifts for (**23c**) are: Me (R^1), δ *ca.* 23; C-3, *ca.* 94; C-4, *ca.* 55; Me (R^2), *ca.* 10 p.p.m.

Mechanistic Pathways.—The observation that methylhydrazine (**3a**) and methyl acetoacetate (**4a**) are completely converted into product (**15a**) exclusively [no (**16a**)] within 10 min after mixing at room temperature indicates that the addition, (**3**) + (**4**) ⟶ (**5**), and also at least one of the three sequences (a)



Scheme 3. ^{13}C N.m.r. assignments

Table 2. Carbon-13 chemical shifts (p.p.m.) of β-ketoesters (**4a**, **c**, **e**, and **g**) (Schemes 1 and 2)[a]

No.	Form	R^1	R^2	R^3	C-1	C-2	C-3	Ref.
(**4a**)	keto	30.8	H	53.1	202.6	50.7	169.3	15*c*
	enol	21.7	H	52.2	177.5	90.5	174.7	16
(**4c**)	keto[b]	28.6	12.8	14.3, 61.6	204.2	53.7	171.1	15*d*
(**4e**)	keto	Ph[c]	H	14.6, 61.9	193.9	46.5	168.5	15*e*
	enol	Ph[d]	H	14.7, 61.3	172.1	88.2	174.1	16
(**4g**)	keto[b]	Ph[e]	14.3	14.5, 62.0	197.1	48.8	171.7	15*f*

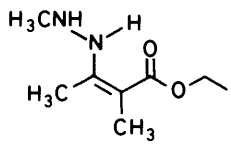
[a] Shifts are relative to CD_3CN at 1.3 p.p.m. [b] No enol tautomer could be detected. [c] Ph: *o*-129.7, *m*-129.3, *p*-134.5, *i*-137.0; *ortho*- and *meta*-assignments are interchangeable. [d] Ph: *o*-129.5, *m*-126.9, *p*-132.3, *i*-134.0. [e] Ph: *o*-129.8, *m*-129.5, *p*-134.5, *i*-136.9; *ortho*- and *meta*-assignments are interchangeable.

Table 3. Carbon-13 chemical shifts (p.p.m.) of 3-pyrazolin-5-ones (**15**),[a] 2-pyrazolin-5-ones (**14**), and (**16**) (Scheme 1)[b]

No.	R	R^1	R^2	C-3	C-4	C-5	Ref.
(**15a**)	31.6	13.0	H	147.5	90.7	161.6	
(**15b**)	Ph[c]	12.6	H	150.7	92.2	162.9	18
(**15c**)	31.3	11.1	7.0	144.9	99.9	163.2	
(**15d**)	Ph[c]	11.4	7.1	148.6	102.7	163.7	19
(**15e**)	33.3	Ph[d]	H	147.8	83.5	153.5	
(**15f**)	Ph[c]	Ph[e]	H	149.9	85.4	154.2	
(**15g**)	32.6	Ph[f]	8.6	146.8	98.6	161.0	
(**15h**)	Ph[c]	Ph[g]	8.5	149.7	102.4	161.4	
(**14b**)	Ph[c]	17.0	H	158.9	43.7	172.3	18
(**14f**)	Ph[c]	Ph[h]	H	156.8	41.0	172.2	
(**16g**)	36.8	Ph[i]	7.7	143.7	99.8	160.6	

[a] Values for compounds (**15**) (NH) reflect a time-averaged equilibrium for (**15**) and its pyrazole (OH) tautomer. [b] Shifts are relative to CD_3CN at 1.3 p.p.m. [c] Peak positions for Ph fall within these ranges: *o*-121.0 ± 1.7, *m*-129.6 ± 0.6, *p*-126.5 ± 1.0, *i*-138.7 + 1.3. [d] Ph: *o*-128.6, *m*-124.8, *p*-127.3, *i*-134.2. [e] Ph: *o*-125.4, *m*-128.7, *p*-128.1, *i*-133.6. [f] Ph: *o*-129.6, *m*-129.4, *p*-129.8, *i*-132.8. [g] Ph: *o*-128.5, *m*-129.8, *p*-129.6, *i*-131.7. [h] Ph: *o*-127.3, *m*-130.1, *p*-130.1, *i*-131.9. [i] Ph: *o*-128.2, *m*-130.4, *p*-129.7, *i*-131.2.

dehydration (**5**) to (**13**) and cyclization (**13**) to (**14**), or (b) dehydration (**5**) to (**9**), isomerization (**9**) to (**13**), and cyclization (**13**) to (**14**), or (c) cyclization (**5**) to (**10**) and dehydration (**10**) to (**14**), proceed rapidly in this instance. This result is not surprising in view of the approximate half-lives measured by Cocivera *et al.*[11] for the analogous reaction involving hydrazine (**3**; R = H) and ethyl acetoacetate (**4**; R^1 = Me, R^2 = H, R^3 = Et) in pH 9 solution: addition, 10^{-4} min, dehydration {[(**9**):(**13**)] 1.8}, 0.3 min, isomerization, 3 min, and cyclization [(**5**) to (**14**) + (**15**)], 1 min.



(**33**)

Pyrazolinone formation is also quite facile in the reaction between (**3a**) and (**4c**); after 15 min no starting materials remain. In addition to product (**15c**), however, the *E*-methylhydrazone (**9c**) is now present in lesser but comparable amount, and its consumption, by the path (**9**) to (**13**)—(**15**), requires an additional 24 h. The essential isomerization, (*E*)-(**9c**) to (*Z*)-(**13c**), is assumed to proceed *via* the enamine tautomer (**33**) and the adverse effect of α-methylation upon this process finds precedent in the much slower rate of deprotonation (aqueous NaOH) of the keto form of ethyl α-methylacetoacetate (**I**) compared with the unbranched parent ester (**II**), $k_{(i)}$ = 200 $k_{(II)}$, as noted by Alcais and Brouillard.[27] We note that other workers[28] report a 10% yield of 2,3,4-trimethyl-3-pyrazolin-5-one (**16c**) along with a 50% yield of (**15c**) after an equimolar aqueous solution of ethyl α-methylacetoacetate (**4c**) and methylhydrazine (**3a**) was heated for 15 h at 70 °C.

When (**3a**) is treated with β-ketoesters (**4e** and **g**), starting materials persist for *ca.* 1 h and *ca.* 1 day, respectively, but no intermediate(s) could be identified. Intermolecular nucleophilic attack by CH_3NHNH_2 is now substantially slower, the benzoyl derivative (**4e**) being much less reactive than the acetyl analogue (**4e**), and so (**3**) + (**4**) to (**5**) becomes the rate-determining step, with α-methylation [as in (**4g**)] further retarding the process. In common with esters (**4a** and **c**), reactant (**4e**) yields a 1-methylpyrazolinone only, *i.e.*, compound (**15e**). From ethyl α-methylbenzoylacetate (**4g**), however, a mixture of pyrazolinone isomers is obtained; here the major product is (**16g**) and the minor one is (**15g**).

Only 1-substituted pyrazolinones (**15**) [plus (**14**) in two cases] are isolated when monosubstituted phenylhydrazine (**3b**) is used. Phenylhydrazone intermediates are detected in each of these reactions, as the decreased basicity and greater steric bulk of NHPh (compared with NHMe) disfavours ring formation, (**5**) to (**14**) and (**13**) to (**14**).

In particular complete consumption of (**3b**) by methyl acetoacetate (**4a**) and ethyl α-methylacetoacetate (**4c**) requires *ca.* 0.5 and *ca.* 1.5 h, respectively, with concomitant formation of a 2:1 mixture of (*E*)-(**9**) and (*Z*)-(**13**) only, in each case. Gradual disappearance of hydrazone (**13b**) produces a detectable amount of product (**14b**) after 3 days, when the ratio (**9b**):(**13b**) is *ca.* 8. Similarly, product (**15d**) appears after 16 h, at which time the steady-state amount of hydrazone (**13d**) is essentially zero, and remains so as the reaction goes to completion.

Within our study, the simultaneous presence of starting materials, intermediate(s), and products is most obvious in the case of the reaction of $PhNHNH_2$ with ethyl benzoylacetate (**4e**) or with ethyl α-methylbenzoylacetate (**4g**). In the β-ketoesters, changing R^1 = Me in (**4a** or **c**) to R^1 = Ph in (**4e** or **g**) should decrease the rate at which nucleophile and electrophile

Table 4. Carbon-13 chemical shifts (p.p.m.) of the 3-pyrazolin-5-ones (**27**) and (**28**) (Scheme 2)[a]

No.	NMe	R	R^1	R^2	C-3	C-4	C-5	Ref.
(**27a**)	33.1	29.0	12.4	H	150.8	94.3	166.0	
(**27b**)	36.0	Ph[b]	13.1	H	159.1	97.7	167.3	20,*e*
(**27c**)	34.2	29.3	10.8	7.3	149.7	103.4	166.8	
(**27d**)	36.6	Ph[b]	11.4	7.5	155.0	105.9	167.4	
(**27e**)	36.4	29.3	Ph[d]	H	156.6	96.8	166.0	
(**27f**)	39.4	Ph[b]	Ph[d]	H	162.2	99.6	166.4	
(**27g**)	36.9	29.5	Ph[d]	8.2	153.9	106.5	166.8	
(**27h**)	39.8	Ph[b]	Ph[d]	8.7	158.0	109.0	167.0	
(**28b**)	30.4	Ph[c]	13.3	H	154.3	97.6	168.1	

[a] Shifts relative to CD_3CN at 1.3 p.p.m. [b] Peak positions for Ph fall within these ranges: *o*-124.8 ± 0.4, *m*-130.0 ± 0.1, *p*-127.4 ± 0.2, *i*-136.5 ± 0.4. [c] Ph: *o*-127.6, *m*-130.7, *p*-129.7, *i*-138.0. [d] Peak positions for Ph fall within these ranges: *o*-130.1 ± 0.8, *m*-129.9 ± 0.4, *p*-129.8 ± 0.2, *i*-130.8 ± 0.8. [e] J. Okada, T. Esaki, and K. Fujieda, *Chem. Pharm. Bull.*, 1976, **24**, 61.

Table 5. Carbon-13 chemical shifts (p.p.m.) of hydrazone intermediates (**9**) and (**13**) (Scheme 1)[a]

No.[b]	R	R^1	C-1(C=N)	R^2	C-2	C-3(C=O)	R^3
(**9b**)	Ph[c]	16.1	141.5	H	45.2	172.7	53.1
(**13b**)	Ph[c]	24.7	141.0	H	37.5	171.0	53.5
(**9c**)	38.2	15.2	147.3	13.2	49.0	174.5	14.7, 61.8
(**9d**)	Ph[c]	14.1	144.7	15.3	49.2	174.5	14.7, 61.9
(**13d**)	Ph[c]	20.2	144.5	13.6	40.6	172.9	14.8, 62.2
(**9f**)	Ph[c]	Ph[d]	141.0	H	44.8	171.3	14.7, 61.8
(**13f**)	Ph[c]	Ph[e]	139.3	H	34.2	170.1	14.7, 61.8
(**9h**)	Ph[c]	Ph[f]	145.3	15.7	48.8	174.2	14.7, 61.7

[a] Values are relative to CD_3CN at 1.3 p.p.m. [b] No intermediates were observed in the conversion of the appropriate β-ketoesters into pyrazolinones (**15a**, **e**, and **g**), respectively; the (*Z*)-hydrazone (**13c**) and *E*-hydrazone (**13h**) could not be detected as well. [c] *ipso* carbon was located at 147 ± 0.6 p.p.m., with signals for the remaining ring carbons being unchanged within experimental error when compared with phenylhydrazine (**3b**) itself. [d] Ph: *o*-126.2, *m*-129.5, *p*-128.8, *i*-134.9. [e] Ph: *o*-126.5, *m*-129.6, *p*-129.0, *i*-138.0. [f] Ph: *o*-126.6, *m*-129.9, *p*-129.0, *i*-134.4.

Table 6. Carbon-13 chemical shifts (p.p.m.) of enamine (**22**) (Scheme 2)[a,b]

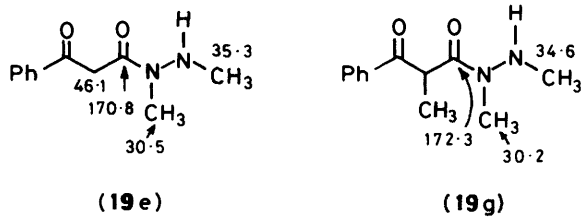
No.[c]	NMe	R	R^1	R^2	C-1	C-2	C-3	R^3
(**22a**)	37.4	35.1	15.3	H	163.6	83.0	170.6	50.4
(**22b**)	39.3	Ph[d]	15.2	H	164.5	85.1	170.5	50.7
(**22f**)	39.6	Ph[e]	Ph[f]	H	164.5	89.4	168.3	14.7, 59.3

[a] Shifts relative to CD_3CN at 1.3 p.p.m. [b] Only one stereoisomer was observed. [c] No intermediates were detected on the reaction pathway(s) to 3-pyrazolin-5-ones (**27c**—**e**) and (**27g**, **h**). [d] Ph: *o*-113.3, *m*-130.4, *p*-120.8, *i*-147.6. [e] Ph: *o*-113.5, *m*-130.5, *p*-120.8, *i*-147.5. [f] *o*-128.8, *m*-130.0, *p*-129.2, *i*-137.0.

combine, (**3**) + (**4**) to (**5**), and destabilize hydrazone (**9**) relative to hydrazone (**13**) (favourable to product formation). Indeed, isomer (**13f**) is the more dominant intermediate [ratio (**13f**):(**9f**) 6] throughout the entire 6 h as the process (**3b**) + (**4e**) to (**5f**) to (**9f**) + (**13f**) to (**14f**) proceeds to completion. As expected, branched substrate (**4g**) reacts quite slowly, requiring 48 h for complete reaction. However, the only detectable (and prominent) intermediate now is the less reactive ethyl α-methylbenzoylacetate (*Z*)-phenylhydrazone (**9h**), and several weeks elapse before it is completely transformed into product (**15h**).

Turning to 1,2-dimethylhydrazine (**17a**) (Scheme 2), we find that it reacts rapidly and completely with methyl acetoacetate (**4a**); only intermediate enamine (**22a**) was present 15 mins after the starting materials were mixed. Product (**27a**) begins to form appreciably within the first hour, but the process (**22a**) to (**27a**) requires *ca.* 4 days for completion. This implies that the necessary isomerization (*E*)-(**22**) to (*Z*)-(**26**) preceding ring closure is quite slow.

No intermediate could be identified within any of the combinations of MeNHNHMe and β-ketoesters (**4c**, **e**, and **g**), respectively, and it seems that here [as with $MeNHNH_2$ + (**4e** or **g**)] the initial addition step [(**4**) + (**17**) to (**18**), Scheme 2] is rate determining. In each instance there is gradual concerted loss of starting materials and appearance of fixed 3-pyrazolin-5-one (**27**) over periods ranging from 3 days (**27c**) to 1 (**27e**) or 2 weeks (**27g**). Within each collection of spectra from a particular combination of reactants there exists an incomplete set of low-intensity peaks. We believe that these peaks can appropriately be assigned to a trace amount of (**23c**) [from (**17a**) and (**4c**), see discussion above for shift assignments], of hydrazide (**19e**) [from (**17a**) and (**4e**)], or of hydrazide (**19g**) [from (**17a**) and (**4g**)], respectively (Scheme 4).



(**19e**) (**19g**)

Scheme 4. ^{13}C Assignments for hydrazides

Reactions involving 1-methyl-2-phenylhydrazine (**17b**) (Scheme 2) require heating at 60 °C to give measurable rates of product formation. This is not unreasonable, given the following reaction times for complete consumption of ethyl benzoylacetate (**4e**) at room temperature: $MeNHNH_2$, *ca.* 1 h; $PhNHNH_2$, *ca.* 2 h; MeNHNHMe, *ca.* 3 days.

In the event almost no β-ketoester (**4a**) and substituted hydrazine (**17b**) remain when a single persistent intermediate (**22b**) is detected after 10 min. Products (**27b**) and (**28b**) gradually accumulate in a ratio of 1:1 over 1 month at 60 °C as enamine (**22b**) is consumed; at 140 °C the ratio (**27b**):(**28b**) becomes 1:3. An earlier synthetic study of the reaction between (**4a**) and (**17b**) at 110 °C gave only product (**28**) in 68% yield.[29] The intervening enamine (**22f**) (R^1 = Ph), never present in relatively large amount during (**4e**) + (**17b**) to (**27f**), apparently isomerizes [(*E*) to (*Z*)] more readily than (**22b**) (R^1 = Me) does, since pyrazolinone formation here is complete within a week.

The rate of formation of product (**27d**) is slightly faster compared with (**27f**) since only traces of (**4c**) and (**17b**) remain after 4 days; however no intermediate(s) could be detected. The slowest by far of the 16 reactions studied involves the most bulky nucleophile (**17b**) and the most sterically hindered electrophile (**4g**); no intermediate ever accumulates and after 1 month at 60 °C formation of product (**27h**) is about one-third complete.

Conclusions.—Most of the 16 reactions clearly proceed by initial nucleophilic attack of the less hindered and more nucleophilic nitrogen of the hydrazine at the ketone carbon atom of the β-ketoester. This pattern is most clearly seen for the reactions of phenylhyrazine (**3b**) where in each case a mixture of phenylhydrazones (**9**) and (**13**) [(**13h**) excepted] is produced. The speed of disappearance of the starting ketoester is in the expected order (**4g**) < (**4e**) < (**4c**) < (**4a**) of the electrophilicity

Table 7. Characterization of pyrazolinones

Compound	R^1	R^2	R	M.p. (°C) Found	Lit.
(15a)	CH_3	H	CH_3	117—118	122—123[a]
(15b)	CH_3	H	Ph	130—131	131—133[a]
(15c)	CH_3	CH_3	CH_3	132—134	133—134[b]
(15d)	CH_3	CH_3	Ph	124—125	123—124[c]
(15e)	Ph	H	CH_3	214.5—215	213—217[a]
(15f)	Ph	H	Ph	136—137	137.5—139.5[a]
(15g)	Ph	CH_3	CH_3	130—132[d]	
(16g)	Ph	CH_3	CH_3	205[e]	
(15h)	Ph	CH_3	Ph	202—203	204—205[f]
(27a)	CH_3	H	CH_3	Oil	(b.p. 104—105 at 0.4 Torr)[a]
(27b)	CH_3	H	Ph	113—114	113—116[a]
(28b)	CH_3	H	Ph	113	113[g]
(27c)	CH_3	CH_3	CH_3	43—45	40—45[h]
(27d)	CH_3	CH_3	Ph	79—80	80.5—82.5[a]
(27e)	Ph	H	CH_3	103—105.5	108[i]
(27f)	Ph	H	Ph	149—150	150[j]
(27g)	Ph	CH_3	CH_3	139—141	141[k]
(27h)	Ph	CH_3	Ph	145—146[l]	

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and steric availability of the keto carbonyl. The rate of ring closure of the hydrazones (**13**) is faster than the formation rate for (**13h**), about the same as the formation rate for (**13f**), and slower for (**13b** and **d**). As expected, the ring-closure rate for the α-methyl derivative (**13d** or **h**) is faster than that for (**13b** or **f**), respectively.

1-Phenyl-2-methylhydrazine (**17b**) reacts with the four keto-esters and, as expected, rates of disappearance of starting materials are in the same order, but much slower, than those found for (**3b**). The cyclization is now much faster than enamine formation for (**22d** and **h**) (consequently not detected), about the same for (**22f**), and much slower for (**22b**). Indeed, in the case of (**22b**), the cyclization rate is so slow that reverse hydrolysis of (**22b**) now occurs to reform (**17b**) and (**4a**); these evidently can also combine slowly to give hydrazide (**20b**), which rapidly cyclizes to give alternative product (**28b**).

In comparison with 1-phenyl-2-methylhydrazine (**17b**), the 1,2-dimethylhydrazine (**17a**) is expected to react faster in both the nuclephilic attack and the ring-formation steps. Although now the symmetrical nature of the reagent does not allow a distinction between products (**27**) and (**28**), the relative rates are readily rationalized on the bases of formation of (**22**) [which is detected in the case of (**22a**)] followed by ring closure (**22**) ⟶ (**26**) ⟶ (**27**). The order of disappearance of starting materials is again the same as in the other two series considered, but only in the case of (**22a**) is the cyclization slower than the reaction forming the intermediate: hence (**22c**, **e**, and **g**) are not seen. Instead, for the benzoyl derivatives (**4e** and **g**) small amounts of the corresponding hydrazides (**19e** and **g**) are detected. Here the steric hindrance evidently encourages some proportion of attack at the ester carbonyl group. In the reaction of (**17a**) and (**4c**), some (**23c**) was detected: (**18**) ⟶ (**23**) competing with (**18**) ⟶ (**22**).

In the methylhydrazine (**3a**) reactions, the rates of disappearance of starting materials follow the usual pattern. The reason for the persistence of (**9c**) has been discussed above; no intermediates were otherwise found. In the (**3a**) + (**4g**) reaction substantial attack also occurs at the ester carbonyl to give (**16g**), probably directed there by steric factors, although why this does not occur in the reaction of (**3b**) with (**4g**) is not clear. [In the case of (**17b**) and (**4g**) we cannot determine whether the reaction occurs by such a pathway.]

Experimental

M.p.s were determined on a Kofler hot-stage and are uncorrected. Combustion analyses were carried out on a Carlo Erba elemental analyser 1106. All reagents were characterized by their ^{13}C n.m.r. spectra, and unless mentioned below, were purchased from Aldrich and used without further purification. Powdered sodium hydroxide was used to liberate *NN'*-dimethylhydrazine (**17a**) from its dihydrochloride salt (Fluka); *N*-methyl-*N'*-phenylhydrazine (**17b**) was prepared through lithium aluminium hydride reduction of *N*-formyl-*N'*-phenylhydrazine.[30]

Spectra.—All ^{13}C n.m.r. spectra were recorded in the temperature range 20—28 °C on a Varian XL-200 spectrometer at 50.32 MHz with full proton decoupling; CD_3CN was used as both internal lock and internal reference. The spectral window was 12 005 Hz with 32 K data giving a digital resolution of 1.0 Hz per point. A pw of 3.6 μs (90°) was used with 0.970 s aquisition time; accumulations varied from 500 to 6 000 per spectrum, giving a typical signal:noise ratio $>10^3:1$.

During the initial period, ^{13}C n.m.r. spectra of reactions were recorded at 15 min intervals with 600 transients per spectrum. This interval was extended to several hours or days as the reaction proceeded. Usually, the accumulation of 600—1 200 transients sufficed to increase signal:noise ratio to $>10^3:1$ but for species in low concentration, long acquisition times were utilized (up to 6 000 transients).

Reactions were started by adding in turn the β-ketoester (**4**) (1.5 mmol), CD_3CN (0.15 ml), and the hydrazine (**3**) or (**17**) (1.5 mmol) to a 5 mm n.m.r. tube; the total volume of solution was *ca.* 0.4 ml, giving an initial concentration of each reactant of *ca.* 3 mol l^{-1}.

Pyrazolinone Synthesis.—In many instances an individual n.m.r. reaction run furnished sufficient product for a confirmatory m.p. determination as well as for an individual ^{13}C n.m.r. spectrum. It was necessary to repeat five combinations on a 10 mmol scale: (i) ester (**4a**) plus hydrazine (**17b**), (ii) ester (**4e**) plus hydrazine (**17b**), and (iii) ester (**4g**) with hydrazines (**3a**), (**3b**), and (**17b**), respectively.

Some compounds were also purchased from Aldrich including 3-methyl-1-phenyl-2-pyrazolin-5-one (**14b**), 2,3-dimethyl-1-phenyl-3-pyrazolin-5-one (**27b**), and 3,4-dimethyl-1-phenyl-3-pyrazolin-5-one (**15d**).

Table 7 contains the m.p.s for all products obtained, plus elemental analyses where appropriate.

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