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The Mechanisms of Heterocyclic Ring Closures

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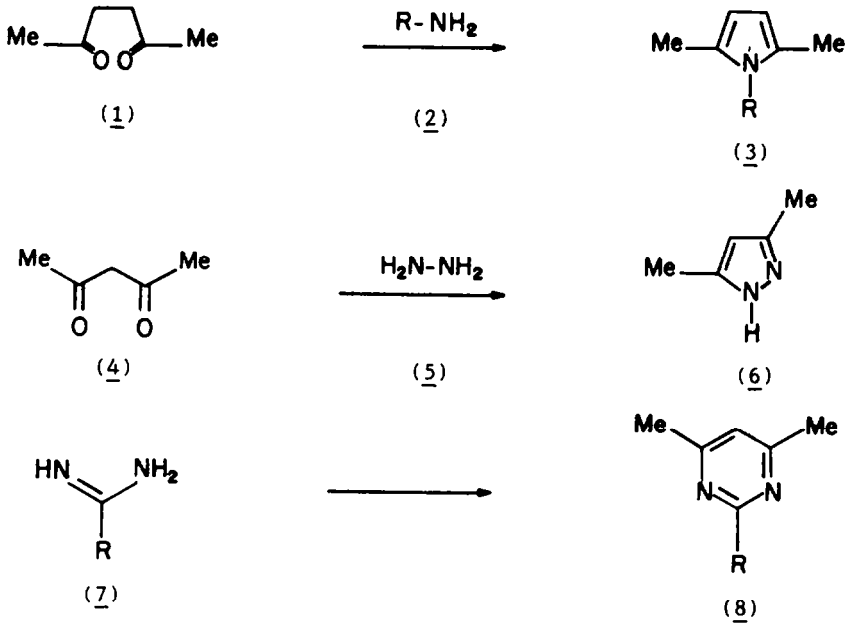
1. Introduction

1.1. Scope

Heterocyclic ring-closures can in general be divided into two large classes: those which involve C-C bond formation and those which do not. The reactions involving C-C bond formation are on the whole, rather well understood mechanistically. These include those proceeding by an electrocyclic mechanism as well as ring closures between electrophilic and nucleophilic carbon centers and between a radical carbon center and a multiple bond.

It is with the other major class of heterocyclic ring closures that the present review is concerned and in particular where a heterocyclic ring is being created from two fragments by the formation of two different carbon heteroatom bonds.

Some of the most common of these reaction types are shown in Scheme 1 with examples: the Paal-Knorr synthesis of pyrroles 3, the formation of pyrazoles 6, and the formation of pyrimidines 8 by the Traube synthesis. These are among the most classical of heterocyclic ring closures, having all been discovered well over a hundred years ago. Their mechanisms are well understood in as far as the individual steps that are involved because of the detailed study of reactions of, for example, amines and hydrazines[1,2] with open chain carbonyl compounds. Nevertheless, amazingly little is known about the detailed sequence of these steps or the nature of the intermediates that occur in such reactions.



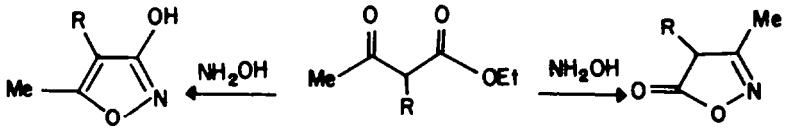
(1) (2) (3) (4) (5) (6) (7) (8)

Scheme 1: Ring Formation From Two Fragments Containing Two Electrophilic Carbon Atoms and Two Nucleophilic Heteroatoms

1.2. Importance

A study of the detailed mechanisms of reactions of this type is important for a number of quite different reasons.

Isomers. Where the two fragments which combine are both unsymmetrical, at least two isomers may be formed in the reactions. In many cases little was known about the reasons for the predominance of one of the isomers, although this predominance can swing wildly from one extreme to another on rather subtle changes in the conditions of the reaction or the structure of the fragments, as illustrated by the case of isoxazolone formation (Scheme 2).[3]



(9) (10) (11)

Scheme 2: The Possibility of Isomer Formations

Optimization of reaction conditions. Knowledge of the detailed reaction mechanisms is expected to be helpful in optimizing the yields in processes of this type. Thus, Broadbent,[4] guided by his deduced mechanism, was able to synthesize by $TiCl_4$ catalysis some highly sterically hindered pyrroles that had hitherto eluded preparation using classical procedures.

Delineation of limits of applicability. Knowledge of these reaction mechanisms should also help in predicting the limits of applicability of such reactions, i.e. for what classes of substituents it can be expected to succeed.

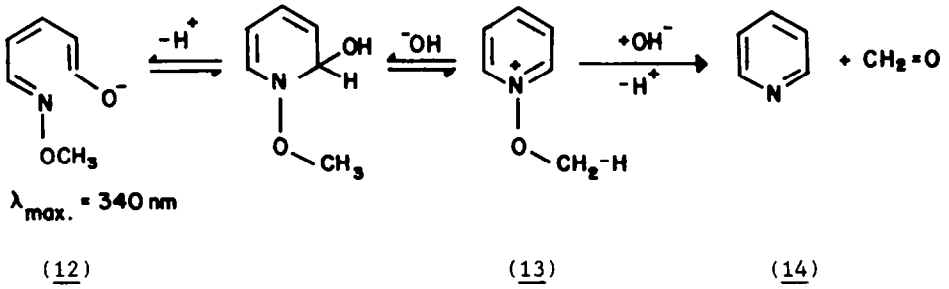
Biosynthetic pathways. Heterocyclic ring forming reactions are also involved in a very large number of biosynthetic pathways as illustrated by the Robinson tropinone mechanism itself.[5] A proper understanding of these mechanisms will enable much speculation on biogenesis to be put on a firmer standing.

1.3. Methods for the Detection of Intermediates

The probable reason for the surprising neglect in the study of the detailed mechanisms of reactions of this type is that they were discovered so early on and investigated in an era when modern spectroscopic methods were unavailable; yet it is just these methods that make the detection of intermediates feasible. Methods that have been used most are infrared and ultraviolet spectroscopy and proton and carbon-13 nuclear magnetic resonance spectroscopy.

Infrared has been used, for example, by Broadbent[4] in his early study of the Paal-Knorr synthesis. The reaction was followed by observing the decrease in intensity of the C=O stretch of the diketone, and appearance and subsequent decrease in intensity of the C=N stretch of the imine intermediate.

Ultraviolet spectroscopy suffers somewhat because it has to be used in very dilute solution: if the intermediate has a low extinction coefficient at the kinetic wavelength, it may not be detected at all. A further drawback is that because UV-absorption peaks are always broad, overlap between peaks may prevent the complete identification of an intermediate. However, in appropriate circumstances, it can be a very powerful technique as illustrated by the study of the conversion of 1-methoxypyridinium cation (13) (Scheme 3) to pyridine (14) by base.[6] The spectra and the fact that the rate of appearance of the strong new peak is proportional to $[OH^-]^2$ suggest the reaction pathways of Scheme 3 with the initial build-up of a reversibly-formed unstable product (12).



(12) (13) (14)

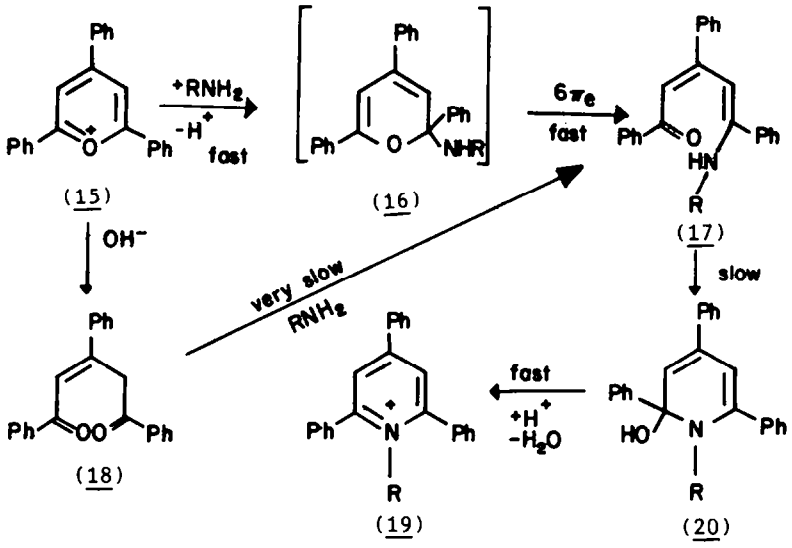
Scheme 3: The Reaction of N-Methoxypyridinium Cation With Hydroxide Anion

The use of nuclear magnetic resonance, and particularly ^{13}C, is emphasized in the present article.

1.4. Kinetics

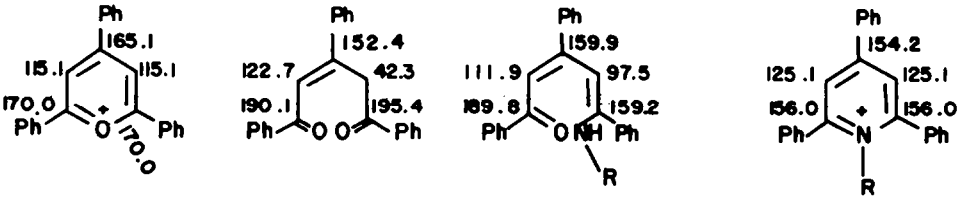
The kinetic study of a reaction can provide valuable insight into its mechanism. Two examples of heterocyclic ring closures studied kinetically are the Paal-Knorr pyrrole synthesis[7] (see discussion in Section 3) and the Radziszewski imidazole synthesis[8].

2. The Pyrylium to Pyridinium Ring Interconversion



Scheme 4: The Reaction Pathway for the Pyrylium to Pyridinium Ring Interconversion

The reaction of primary and secondary amines with 2,4,6-triphenylpyrylium cation (15) (Scheme 4) is shown by ^{13}C nmr to proceed by fast ring opening to a vinylogous amide (17), which, in the case of primary amines, closes slowly to a pyridinium cation[9] (19) (Scheme 4). The ring carbon atom shifts for the various species (pyrylium, pyridinium, diketone, vinylogous amide) are all distinct (see Scheme 5), and this allows the reaction to be followed by C-13. As no signals are detected for 16 or 20, steps 16 --> 17 and 20 --> 19 are fast. If water is present, hydrolysis 15 --> 18 competes; 18 reacts further, but very slowly.

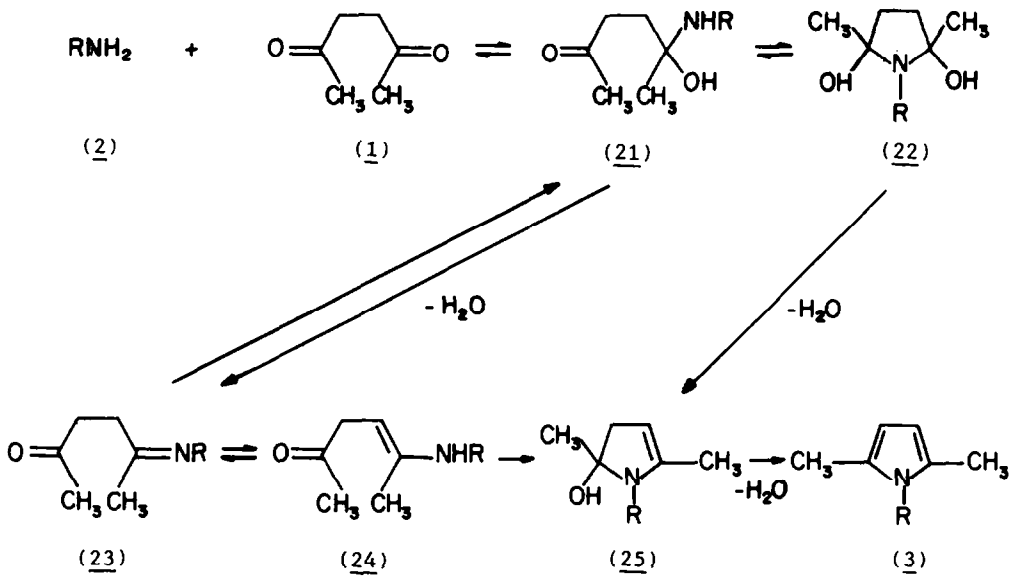


Scheme 5: ^{13}C-NMR Assignments of Ring Carbon Atoms in the Pyrylium to Pyridinium Conversion

3. The Paal-Knorr Synthesis of Pyrroles

The Paal-Knorr synthesis is one of the most important preparative methods for pyrroles.[10,11] It involves the reaction of a primary amine with a 1,4-diketone with elimination of two molecules of water. Possible mechanistic paths for this reaction are shown in Scheme 6. There are two main alternatives: the first involves formation of the imine (23) and enamine (24) as intermediates, and second involves the intermediate formation of the 2,5-dihydroxypyrrolidine (22). Neither of these mechanisms is discussed in the two definitive monographs on pyrroles.[10,11] Borche and Fels[12] suggested early that ring closure occurred in the enamine (24) and its tautomer, the imine (23), was subsequently detected by Broadbent.[4]

Sundberg[13] in his recent review favored the intermediacy of the 2,5-dihydroxypyrrolidine (22), as does Tseng following a detailed kinetic[7a, b, c] and ^{1}H nmr[14] study of this reaction.

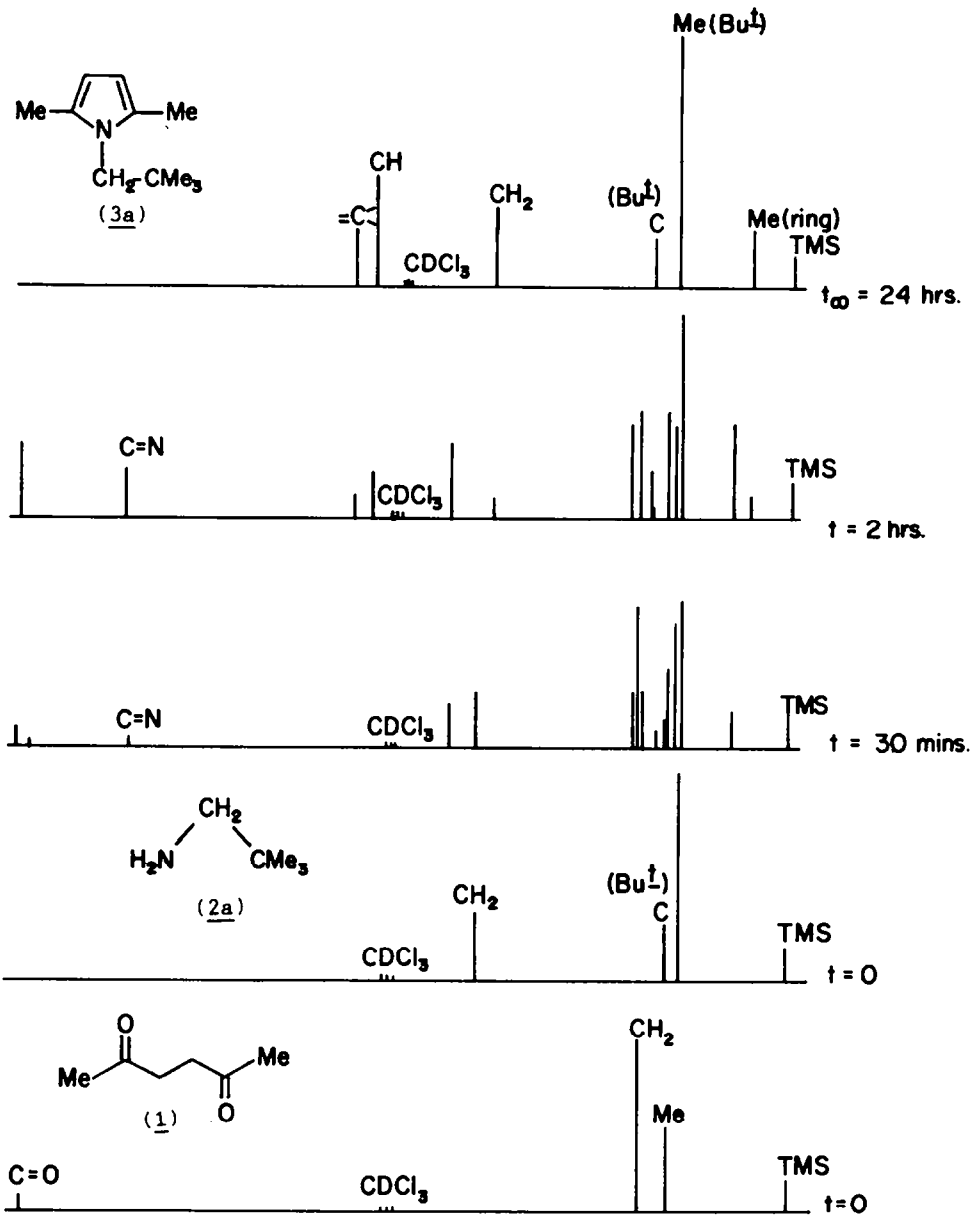


Scheme 6: Alternative Mechanistic Pathways for the Paal-Knorr Reaction

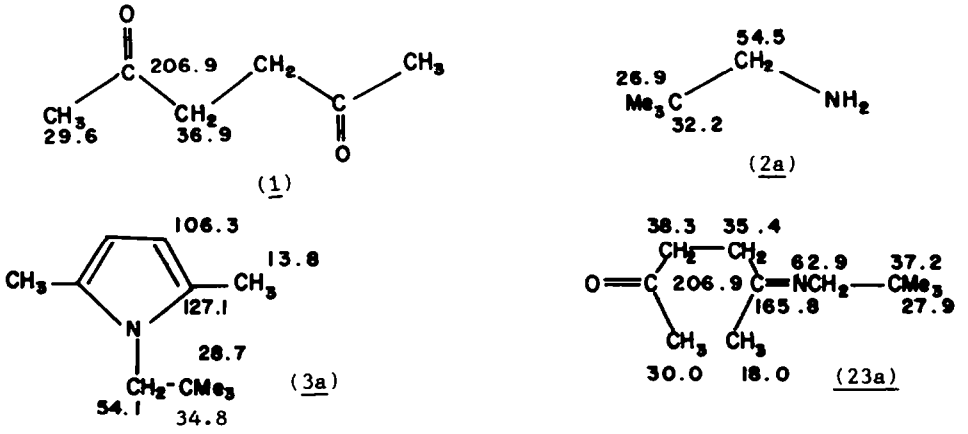
The reaction displays excellent first-order kinetics in alkaline media (pH 9) and second-order kinetics in acidic media (pH 1), with a fractional order pertaining at intermediate pHs.[7] It also has the characteristics of a typical carbonyl addition reaction[15]: a bell-shaped graph of rate-constant versus reaction pH; a large, negative entropy of activation (Delta S^{+} = -50 cal $mol^{-1}k^{-1}$ and a small, positive enthalpy of activation (Delta H^{+} = +8 k cal mol^{-1}), and it obeys three linear free energy relationships: the isokinetic relationship (beta = 394.9°), the Hammett equation (rho^{+} = -0.88), and the Bronsted equation (alpha = 0.25). The interpretation of the kinetic data in acidic media is straightforward: nucleophilic attack of the free amine 2 on the carbonyl carbon of acetylacetone 1 is rate-determining (Scheme 6). In basic media however, the rate law would be consistent with the intermediacy of both the diol 22 (Scheme 6) and the imine (23). Hence, the kinetic study does not allow a clear differentiation between the two alternative pathways of Scheme 6.

Our ^{13}C nmr study of the Paal-Knorr reaction[16] showed distinct peaks for an intermediate, which appeared, grew to a maximum and then disappeared as the product pyrrole was produced. An example of this is shown in Scheme 7. The corresponding ^{13}C chemical shift assignments are shown in Scheme 8; those for starting materials and product are also given and were confirmed using authentic specimens. The assignments for the intermediates seen in both reactions can be interpreted only on the basis that they are imines and not dihydoxypyrrolidines: this follows both from the chemical shifts and from the number of peaks observed.

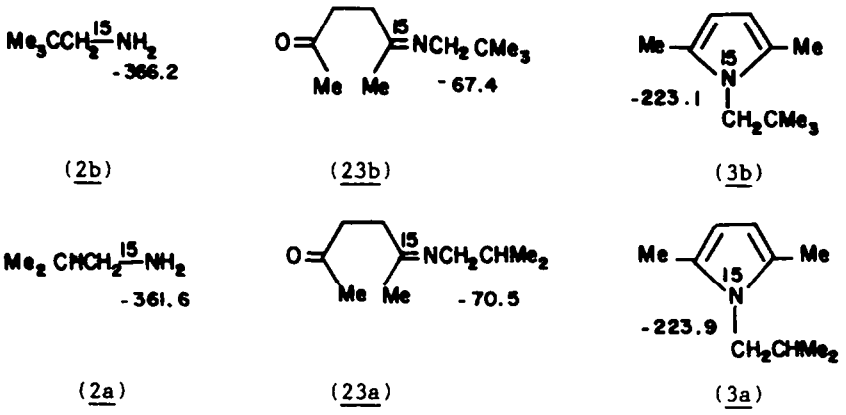
These conclusions are confirmed by ^{15}N and ^{1}H nuclear magnetic resonance: examples of the ^{15}N chemical shifts of starting materials, intermediates and products are given in Scheme 9 (the chemical shifts quoted are relative to external nitromethane).



Scheme 7: ^{13}C NMR Spectra of the Reacting of Acetonylacetone (1) with Neo-Pentylamine

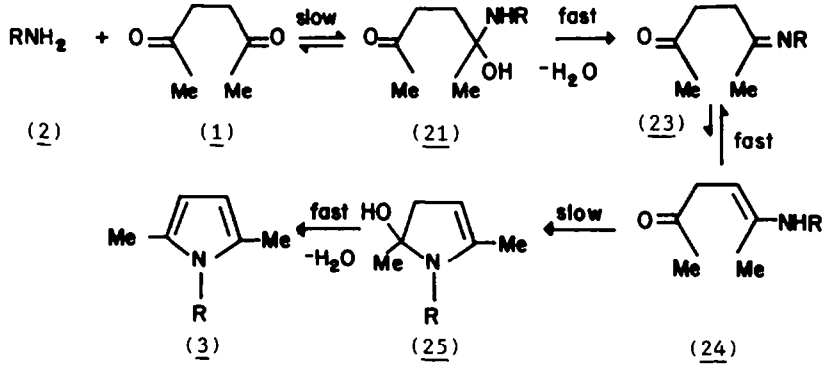


Scheme 8: ^{13}C NMR Assignments and Chemical Shifts in ppm of Starting Materials (1) and (2a), Intermediate (23a and Product (3a) in the Paal - Knorr Reaction



Scheme 9: ^{15}N NMR Assignments and Chemical Shifts in PPM of Starting Materials, Intermediates and Products in the Paal-Knorr Reactions

We can therefore now designate the dominant reaction pathway for the production of the pyrroles in the Paal-Knorr synthesis together with the slow and fast steps along it as depicted in Scheme 10.



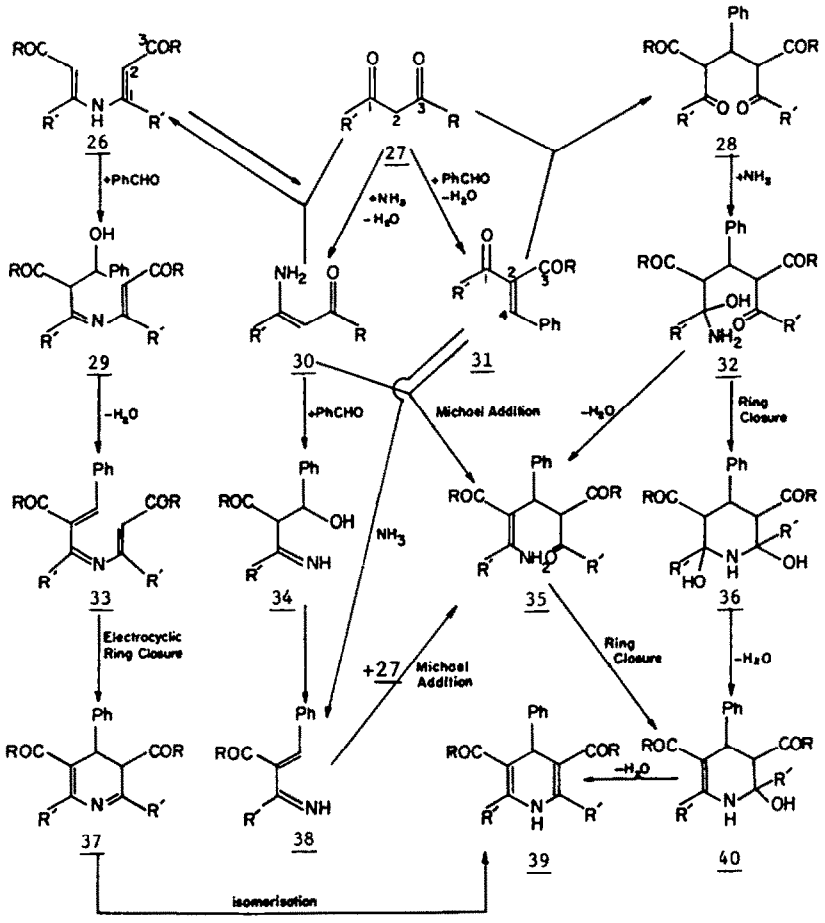
Scheme 10: The Mechanism of the Paal-Knorr Reaction

4. The Hantzsch Dihydropyridine Synthesis

The oldest classical synthesis of dihydropyridines, due to Hantzsch[17], is the reaction of a 1,3-dicarbonyl compound with an aldehyde and an amine or ammonia. The reaction has generally been assumed to proceed via the intermediacy of the aminocrotonate 30 and the alpha, beta-unsaturated ketone 31 or the dihydroxypiperidine 36 (Scheme 11).[18]

Following an extensive study of dihydropyridine synthesis, Berson[19] favoured the aminocrotonate (30, R=OMe) pathway, as did Marsi[20], who also considered the dienamine 26 pathway but rejected it on the grounds that imine type intermediates could not be isolated from the reaction medium. More recently, diols of type 36 have been isolated in high yields by Singh[21] in the exceptional case of the reaction of 4,4,4-trifluoroacetoacetate (Cf 27, R=OMe, R'=CF_3) with a range of substituted benzaldehydes; however, the subsequent conversion 36--->40--->39 did not occur, even in the presence of strong dehydrating agents.[21]

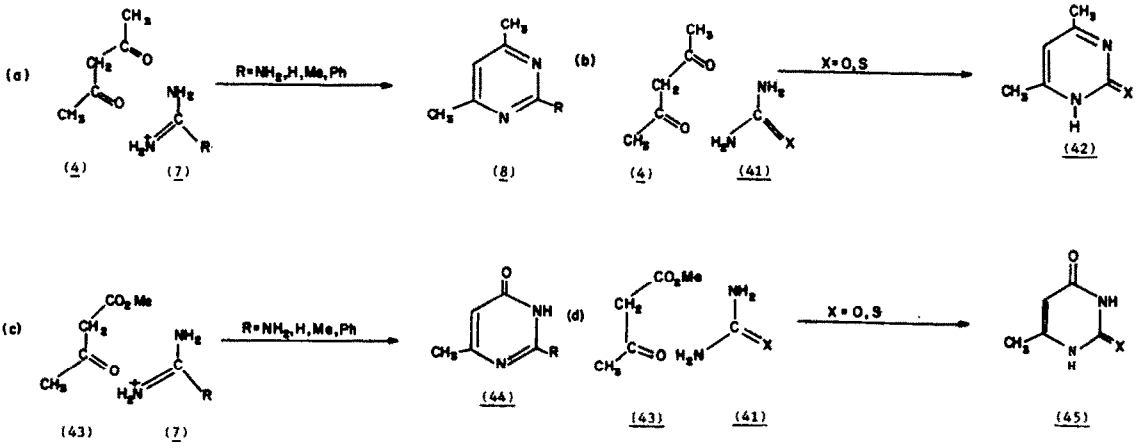
We have investigated by C-13 and N-15 nmr spectroscopy two versions of the Hantzsch dihydropyridine synthesis[22]: the reactions of two beta-diketones (27, R=R'=Me and R=Ph, R'=Me) and one beta-ketoester (27, R=OMe, R'=Me) with benzaldehyde and ammonia. All the reactions showed the enamine 30 and the chalcone 31 as intermediates on the pathway to product 39, with Michael addition of 30 to 31 being the rate determining stage. None of the intermediates on the alternative reaction pathways [(ii): 27 --> 28 --> 39, (iii): 27 --> 26 --> 39, (iv): 27-->34-->39] were observed. Peaks characteristic of metastable sideproducts (dienamines) 26 were observed in the early stages of the reaction of the diketones with benzaldehyde and ammonia.



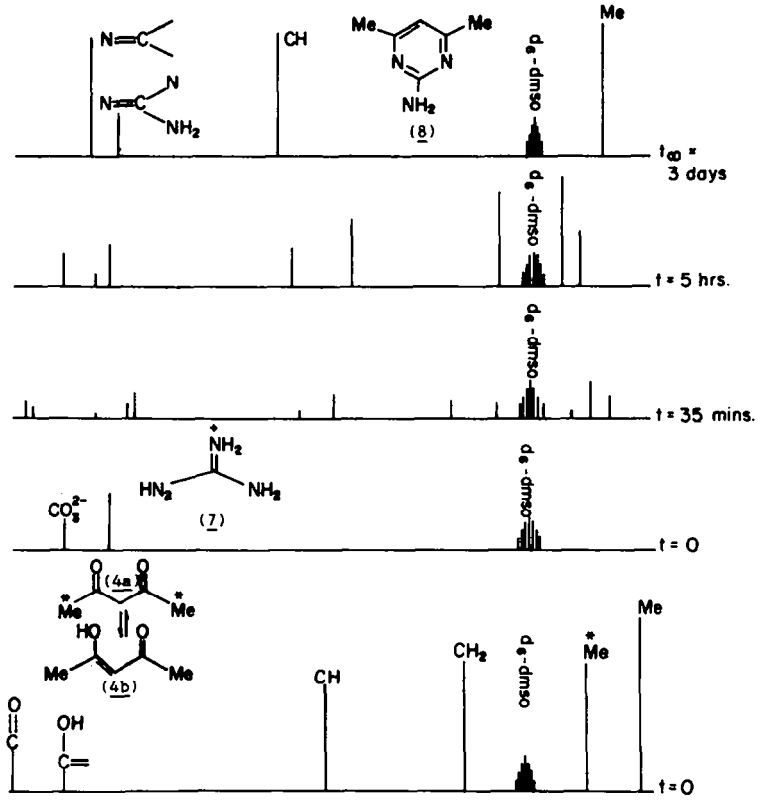
Scheme 11: Reaction Pathways for the Hantzsch Synthesis of Pyridines

5. Formation of the Pyrimidine Ring by the Traube Synthesis

We have investigated a total of sixteen examples encompassing six structural types of the Traube synthesis.[23] Four types showed characteristic intermediates (Scheme 12): (a) reaction of the beta-diketone acetylacetone (4) with amidines (7); (b) reaction of (4) with urea and thiourea; (c) reaction of the beta-ketoester, methyl acetoacetate (43) with amidines (7); (d) reaction of (43) with urea and thiourea.

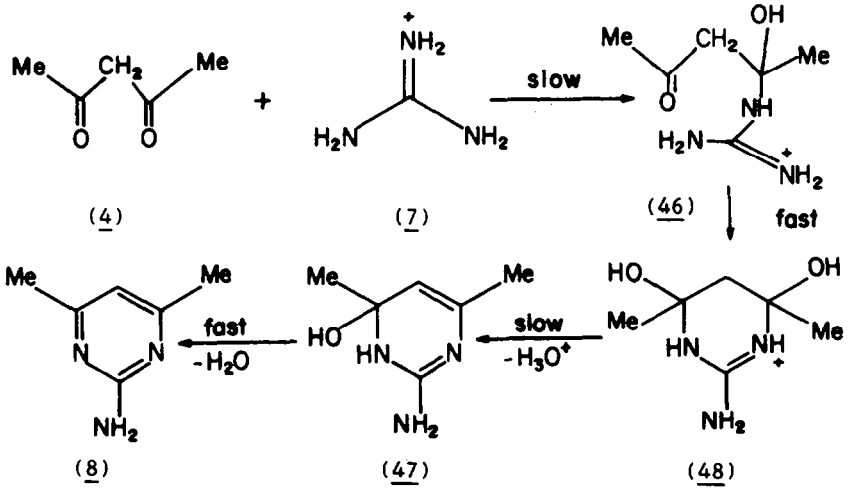


Scheme 12: Types of Pyrimidine Synthesis Investigated



Scheme 13: ^{13}C NMR Spectra of the Reaction of Acetylacetone (4) With Guanidine Carbonate (7)

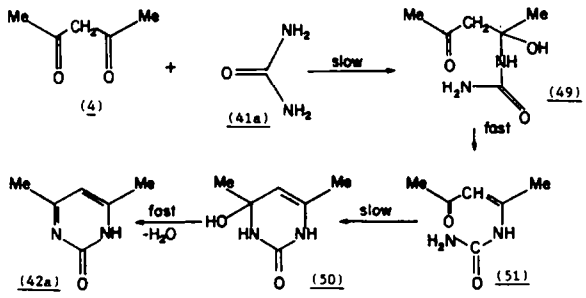
An example of a reaction of type (a) is given in Scheme 13. We see the formation of an intermediate, demonstrated by its ^{13}C spectrum to be the tetrahydropyrimidine-4,6-diol (48). The absence of peaks characteristic of other intermediates indicates the pathway of Scheme 14, with fast ring closure of the carbinolamine (46) to form the diol (48), followed by two successive eliminations, of which the 48--->47 is rate determining, to give product (8).



Scheme 14: The Mechanism of the Reaction of Acetylacetone (4) with Guanidine Carbonate (7)

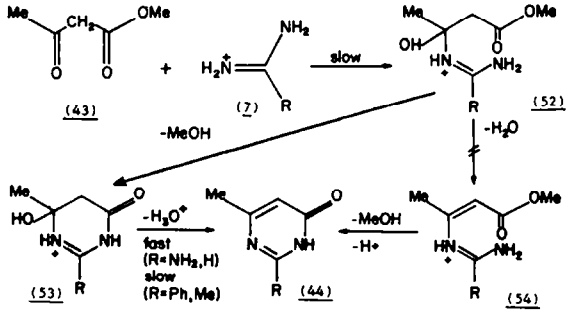
By contrast, reactions of type (b) show a different intermediate, characterized spectrally as the enamide (51) (Scheme 15). The overall ring synthesis therefore involves the pathway shown, in

which elimination from the carbinolamine (49) to form the enamide (51) is now faster than competitive ring closure of the carbinolamine 49.



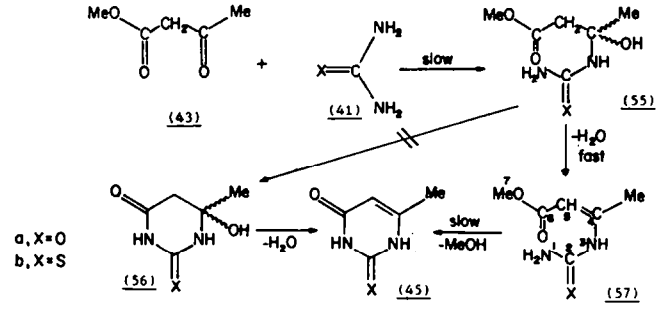
Scheme 15: The Mechanism of the Reaction of Acetylacetone with Urea (41a)

The pathway for reactions of type (c) is as shown in Scheme 16. We have used four different amidines (7) in this reaction. In all cases one intermediate is found: however, with R = H or NH_2, we assign the intermediate the open chain structure (52), characterised by the presence of a methoxycarbonyl group, whereas for R = Me or Ph we believe that the intermediate has the closed hydroxytetrahydropyrimidinone structure (53) (Scheme 16). The chemical shifts of the intermediates are similar but a vital and characteristic difference is the concomitant formation of MeOH when R = Ph or Me and ring closure is fast. All the reactions were carried out at pH 10 - 12; the difference in mechanism (Scheme 16) apparently depends on conformational changes in substituent R.



Scheme 16: The Mechanism of Reaction of Methyl Acetoacetate (43) with Guanidine and Benzamidine (7)
Step 52 --> 53 is slow for R = NH_2 or H, but fast for R = Ph or Me

Reactions of type (d) (Scheme 17) are mechanistically similar to those of type (b): i.e., the initially formed carbinolamine (55) readily eliminates water to give the aminocrotonate (57) which undergoes slow ring closure to the pyrimidin-dione (45) (Scheme 17).

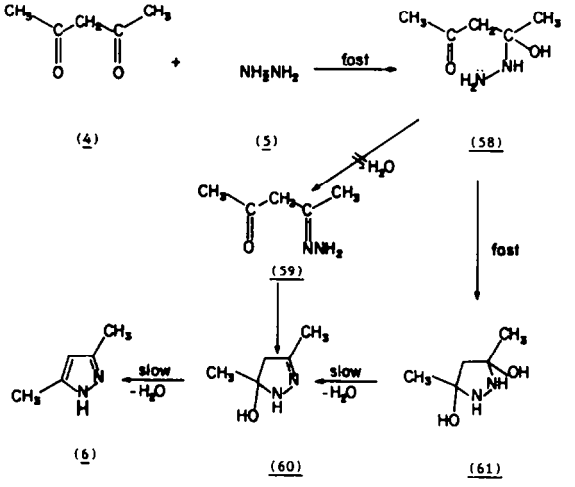


Scheme 17: The Mechanism of Reaction of Methyl Acetoacetate (43) with Urea (41a) and Thiourea (41b)

In reactions of dimethyl malonate with formamidine, benzamidine, urea or thiourea, no intermediates were seen during the course of the reaction. The implication of this is that in all these cases ring closure is faster than the initial nucleophilic attack.

6. The Synthesis of Pyrazoles and Isoxazoles from 1,3-Diketones

Selivanov has reported [24a,b,c] that the reaction of 1,3-diketones with methylhydrazine and hydrazine involve formation of dihydroxypyrazolidine intermediates (61) (Scheme 18) as shown by proton nmr stop-flow techniques. No evidence was found for hydrazone intermediates (59); instead, the first addition product (58) of the hydrazine with one of the carbonyl groups of the 1,3-diketone 4 immediately cyclizes; intermediate diol (61) then undergoes two successive eliminations to give product (6), and the second of these eliminations is rate determining.



(4) (5) (58) (59) (6) (60) (61)

Scheme 18: The Mechanism of Reaction of Acetylacetone (4) with Hydrazine (5) or Hydroxylamine

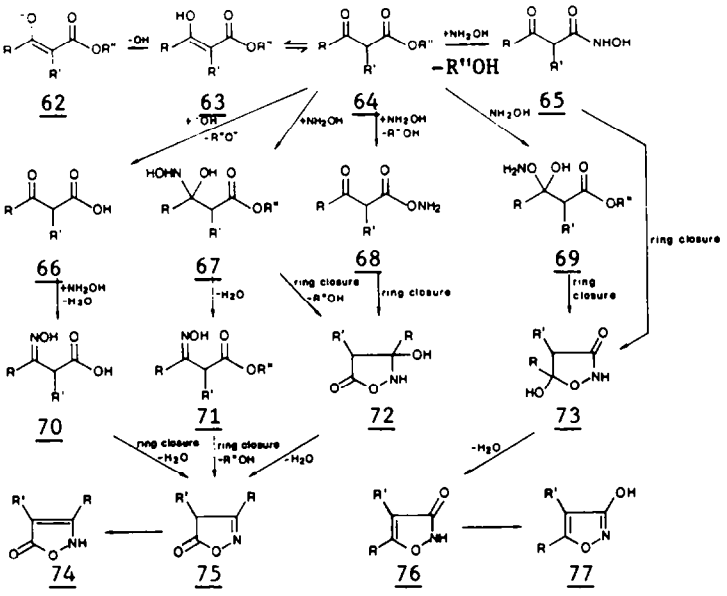
The diketone (4) (Scheme 18) may in principle react in either the keto or the enol form. The authors give ^{1}H nmr evidence for reaction via the keto form, showing that the enol form does not react, but complexes, with hydrazine; indeed, at low temperatures the rate determining step is reformation of the diketone from the enol-hydrazine complex. An analogous complex was shown to form with morpholine, a base with a pK_a similar to that of hydrazine. In the case of unsymmetrical beta-diketones, the simultaneous presence of the dihydroxypyrazolidine (61) and two distinct hydroxypyrazolines (cf 60) as intermediates in the reaction mixture was detected by ^{1}H nmr.

A similar, but more detailed study of the reaction of acetylacetone 4, with hydroxylamine has been carried out by Cocivera et al,[25] by continuous flow and stopped-flow ^{1}H-nmr spectroscopy. First- and second-order rate constants were obtained by observing the broadening of the peaks and then applying nmr line shape analysis to this broadening. Rapid formation of the diol (cf 61 in Scheme 18), k(4 ---> 61') = 2.3 x 10^3 s^{-1}, in phosphate buffer in the pH range 7.3-8.0, was followed by slow elimination, k(61' ---> 60') = 2.7 x 10^{-3} s^{-1} (pH8.0), to yield the hydroxyisoxazoline 60'. The rate-determining step at alkaline pH is the second elimination 60' ---> 6'. The absence of peaks due to the oxime (cf 59) is evidence that elimination from the carbinolamine (cf 58) is much slower than the ring closure (cf 58 ---> 59, just as in the mechanism of pyrazole formation (cf Scheme 18).

In the pH range 1.5-3.0, the elimination is now general acid catalysed and the authors suggest[25] that now the rate-determining step is the initial nucleophilic attack of free hydroxylamine on acetylacetone 4 (k_2 = 4.5 x 10^2 ($mol^{-1}s^{-1}$ at pH 3.0)) followed by fast elimination to give a mixture of the syn and anti oximes. As neither of these oximes were detected, the authors proposed fast subsequent ring closure.

7. Isoxazolone Syntheses from beta-Ketoesters

The condensation of a beta-ketoester (64) with hydroxylamine could occur in two directions: to give (i) an isoxazolin-5-one (74) or (ii) an isoxazolin-3-one (76) (Scheme 19). Although early workers[26-29] considered the single product isolated from each reaction to be an isoxazolin-5-one (74), it is now known that mixtures of 74 and 76 are produced in general[30,31], with the actual yields of the two isomers depending upon the pH regimen used.

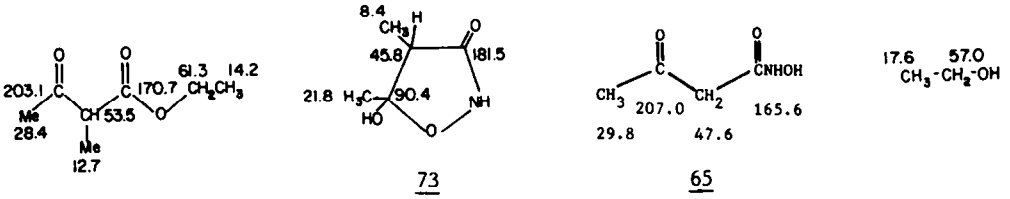


Scheme 19: The Mechanism of the Reaction of Hydroxylamine with beta-ketoesters

In a detailed ^{1}H nmr investigation of the reaction of ethyl acetoacetate (64, R=CH_3, R'=H, R''=C_2H_5, Scheme 19) with hydroxylamine in the pH range of 6.5 to 8.5 (buffered), Cocivera et al[32] identified 3-methylisoxazolin-5-one 74a (Scheme 19) as the only heterocyclic product; under stop-flow conditions they were able to detect the initial carbinolamine 67 (R=CH_3, R'=H, R''=C_2H_5) intermediate which underwent subsequent dehydration to form syn and anti oximes (71). The syn isomer (R=CH_3, R'=H, R''=C_2H_5) cyclized within several minutes to form product 74, but conversion of the anti form to isoxazolinone 74 required several hours. The absence of peaks due to the protons of hydroxyisoxazolidinone 72 (Scheme 19) implies that elimination from carbinolamine 67 is faster than the ring closure 67-->72.

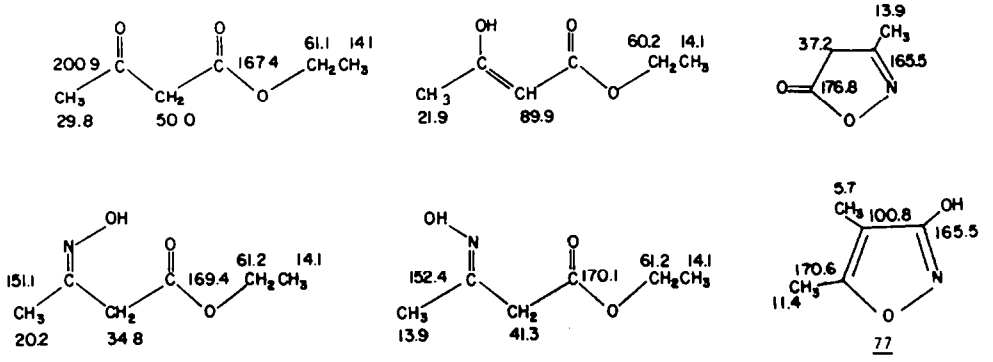
Our observation (^{13}C nmr)[3] of product 75 (O^- form) in the reactions of each of three esters 64 (R=R'=R''=Me; R=R''=Me, R'=H; R=PR, R'=H, R''=Me) with hydroxylamine at pH 10 and pH 12 is consistent with the pathway, 64-->67-->71-->75 (Scheme 19) established above; the presence of a persistent anti form of oxime 71 could not, however, be confirmed. We also noted in the spectra of the basic reaction mixtures in every instance predominant peaks corresponding to intermediate (s) 73 and/or open chain hydroxamic acid 65.

Our own ^{13}C NMR study has now clarified the manner in which 3-hydroxyisoxazole 77 (Scheme 19; isoxazolin-3-one 76 is the minor tautomer in solution[33]) is formed; it involves dehydration of the 5-hydroxyisoxazolidin-3-one 73 under highly acidic conditions. Quenching of the fresh pH 10 or pH 12 reaction mixture in excess cold concentrated hydrochloric acid causes the process 65-->73-->76-->77 to occur, thereby accounting for the high yields of 3-isoxazolols 77 reported in recent synthetic studies by Jacquier et al[30] and Jacobsen et al.[31] When these same two groups of workers gradually acidified the basic reaction mixtures more slowly to pH 2-5, isoxazolin-5-ones 75 (rather than the 3-isoxazolols 77) were the major products. Our spectral results[3] indicate that at pH 2 and above intermediate 65 (73 is completely converted to 65 at pH 3) reacts with catalytic amounts of residual hydroxylamine (i.e. 65 + NH_2OH-->oxime of 65--> 75 + NH_2OH) to augment the stable isoxazolinone 75 which had already formed (along with 65 and/or 73) in basic solution.



Scheme 20: ^{13}C NMR Assignments and Chemical Shifts in PPM for Intermediates of Type (65) and (73) in Isoxazole Synthesis.

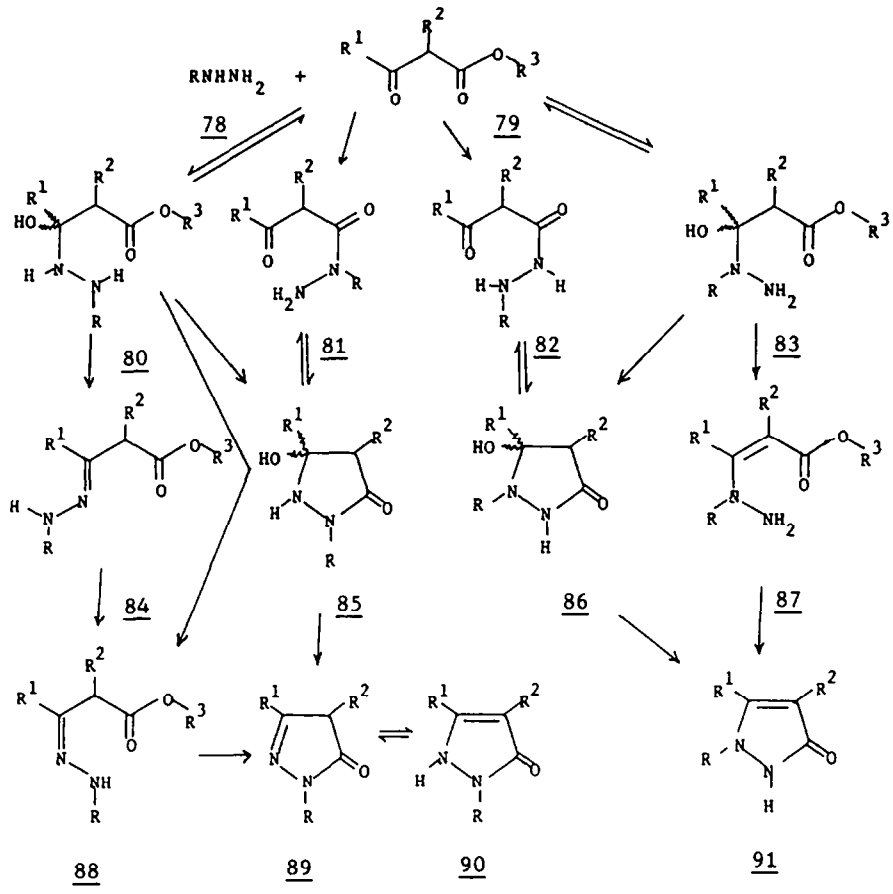
The ^{13}C NMR chemical shifts of some of the intermediates 65 and 73 and products 75 and 77 are assembled in Schemes 20 and 21, respectively. Because intermediates 65 and 73 exist in dynamic equilibrium under our conditions, and no evidence for species 69 was obtained, our work does not establish which one, i.e., 65 or 73, forms first.



Scheme 21: ^{13}C NMR Assignments and Chemical Shifts in PPM for Products of Type (75) and (77) in Isoxazole Synthesis.

8. The Synthesis of Pyrazolones from beta-Ketoesters

Cocivera, Woo, and Livant[34] have shown by proton nmr stop-flow techniques that conversion of hydrazine (78, R=H) and ethyl acetoacetate (79, R^1=CH_3, R^2=H, R^3=C_2H_5) into 3-methylpyrazolin-5-one (89, R=R^2=H, R^1=CH_3) proceeds through the intermediate carbinolamine 80, thence to hydrazone 88 (R=R^2=H, R^1=CH_3, R^3=C_2H_5), which then ring closes to give product 89 (Scheme 22). No additional intermediates, other than hydrazone 84, were detected by these workers. Approximate half lives for the steps in the reaction between hydrazine and ethyl acetoacetate were: addition, 78 + 79 to 80, 10^{-4} min; dehydration, 80 to 84 + 88, 0.3 min; isomerization, 84 to 88, 3 min; and cyclization, 80 to 89, 1 min.



Compd:	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

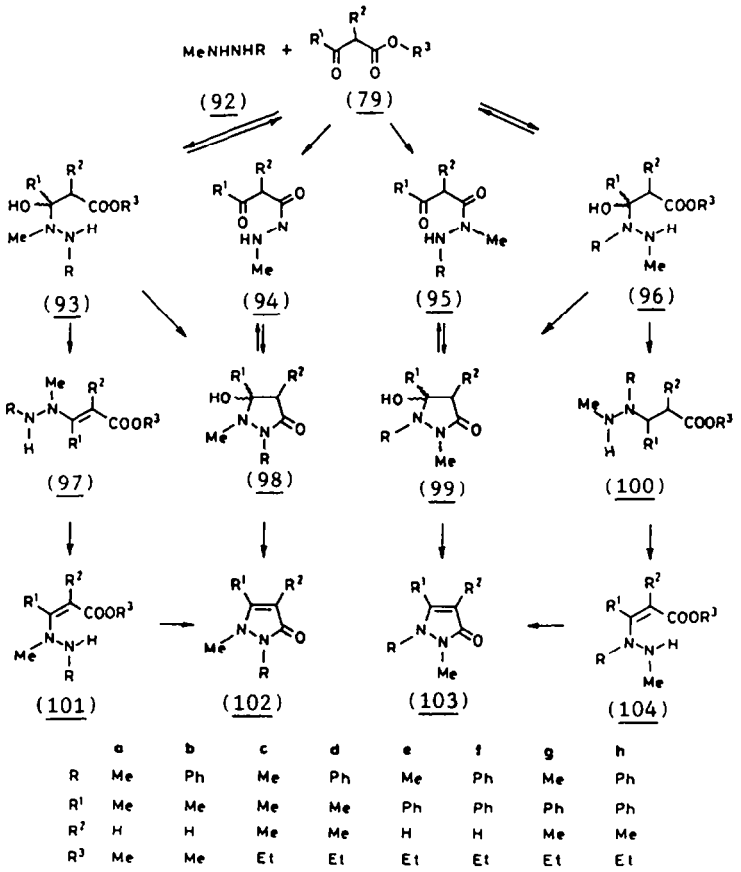
Scheme 22: The Mechanism of the Reaction of Methylhydrazine and Phenylhydrazine with beta-Ketoesters.

Subsequently we followed all possible reactions between each of four hydrazines (methyl-, phenyl-, 1,2-dimethyl-, and 1-methyl-2-phenyl-hydrazine) and four beta-ketoesters 79a, c, e, g by ^{13}C nmr spectroscopy.[35]

Most of the sixteen pairs studied clearly proceed by initial nucleophilic attack of the less hindered (and more nucleophilic) nitrogen of the hydrazine at the ketonic carbon of the beta-ketoester. This pattern emerges most clearly in the reactions of phenylhydrazine 78b (Scheme 22), where in each instance a mixture of the phenylhydrazones 84 and 88 (88h excepted) is detected on the way (Scheme 22) to the 1-phenylpyrazalinones 89 and/or 90 (R=Ph). The rates of loss of the starting beta-ketoesters 79 is in the expected order: 79g < 79e < 79c < 79a of the electrophilicity and steric availability of the ketone carbonyl. The rate of ring closure of hydrazone 88 is faster than the formation rate for (the non-detectable) 88h, about the same as the formation rate for 88f, and slower for 88b and 88d. Once formed, alpha methyl derivatives 88d and 88h as expected both cyclize faster than either 88b or 88f.

With methylhydrazine 78a, the rates of disappearance of starting esters 79 are somewhat faster than those found for 78b, although in the same order. No intermediates were detected on the ^{13}C nmr time scale with esters 79a, e, and g; exceptionally the metastable hydrazone 84c (Scheme 22 $R=R^1=R^2=CH_3$, $R^3=C_2H_5$) was observed during the reaction of ethyl alpha-methylacetoacetate 79c with 78a. Exclusive formation of products 90a, 90c, and 90e (no 91) from the corresponding esters 79 implies that in each case hydrazone 88 ($R=CH_3$) lies on the favored reaction pathway. The combination of 78a and ethyl alpha-methylbenzoylacetate 79g yields a mixture of the pyrazolinone isomers 91g (more) and 90g (less). Here substantial attack occurs at ester carbonyl (78a + 79g -- >82g, Scheme 22) to give the major product, probably directed away from ketonic carbon by steric factors, although why this does not extend to the reaction of 78b with 79g is not clear.

The symmetrical nature of dimethylhydrazine 92a means only one product (Scheme 23, $R=CH_3$, 102 and 103 are then identical) is possible in this series. The order of consumption of starting materials is the same as in the prior two sets, and relative rates for 92a plus esters 79 are readily understood on the basis of the formation of enamine 97 (detected in the case of 97a) followed by ring closure 97 to 101 to 102 (Scheme 23). Intermediates 97c, e, and g are not seen, since the reaction forming the enamine is faster than subsequent cyclization only in the case of 97a. Minor amounts of intermediate hydrazides 94e and 94g are detected instead for benzoyl derivatives 79e and 79g. In the reaction of 92a and 79c, some 98c was found: 93 to 98 competing with 93 to 97 (Scheme 23).



	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 23: Mechanism of the Reaction of 1,1-Dimethylhydrazine and 1-Methyl-2-phenylhydrazine with beta-Ketoesters.

Reactions involving 1-methyl-2-phenylhydrazine 92b (Scheme 23) require heating at 60°C to give measureable rates of product formation, the rates of disappearance of starting materials following the usual pattern. Intermediate enamine 97b is produced rapidly and completely from methyl acetoacetate 79a, thereafter being gradually transformed into an 1:1 mixture of products 102b and 103b. The remaining three esters 79c, e, b lead only to products 102. Cyclization (97 to 102) is much faster than enamine formation for 97d and 97h (therefore not detected), about the same for 97f, and much slower for 97b. In the case of 97b, direct cyclization must compete with reverse hydrolysis to reform starting materials; apparently 92b and 79a can also combine slowly to give hydrazide 95b (not detected), which rapidly ring closes to yield alternative product 103b.

References

1. S. Dayagi and J. Degani in, "The Chemistry of the Carbon-Nitrogen Double Bond", ed. S. Patai, Interscience, N.Y., 1970, pp. 64-83.
2. R.L. Reeves in, "The Chemistry of the Carbonyl Group",ed. S. Patai, Interscience, N.Y., 1966, Vol. 1, pp. 600-614.
3. A.R. Katritzky, P. Barczynski, D. L. Ostercamp, and T.I. Yousaf, J. Org. Chem., 51, (1986) 4037.
4. H.S. Broadbent, W.S. Burnham, R.K. Losen and R.M. Sheeley, J. Heterocyclic Chem. 5, (1968) 757.
5. R. Robinson, J. Chem. Soc., 111, (1917) 762.
6. A.R. Katritzky and R. Eisenthal, Tetrahedron, 21, (1965) 2205.
7. (a) Tseng Kuang-Chih, Yan Jia-Sheng and Shen Ding-Zhang, Acta Chemica Sinica, 39, (1981) 215; (b) Tseng Kuang-Chih, ibid., 40, (1982) 720; Tseng Kuang-Chih, ibid., 32, (1966) 107.
8. Y. Ogata, A. Kawasaki and F. Sugiara, J. Org. Chem. (1969), 34, 3981.
9. A.R. Katritzky, R.T.C. Brownlee and G. Musumarra, Tetrahedron, 36, (1980) 1643.
10. R.A. Jones and G.P. Bean, "The Chemistry of Pyrroles", ed. A.T. Bloomquist and H.H. Wasserman, Academic Press, London, 1977, pp. 77-79
11. A. Gossauer, "Die Chemie der Pyrrole", Springer Verlag, Berlin, 1974, pp. 239-244.
12. W. Borsche and A. Fels, Ber., 39, (1906) 3877.
13. R.J. Sundberg in, "Comprehensive Heterocyclic Chemistry", ed. A.R. Katritzky and C.W. Rees, Pergamon Press, Oxford, 1984, Vol. 4, p. 329-330.
14. Tseng Kuang-Chih, personal communication.
15. R.W. Alder, R. Baker and J.M. Brown "Mechanism in Organic Chemistry", Wiley-Interscience, England, 1970, p 321.
16. A.R. Katritzky, T.I. Yousaf, Ban Chi Chen and Tseng Kuang-Chih, Tetrahedron, 42, (1986) 623.
17. A. Hantzsch, Liebigs Ann. (1882), 215.
18. G. Jones in "Comprehensive Heterocyclic Chemistry", A.R. Katritzky and C.W. Rees (eds); Pergamon Press, Oxford, 1984, Vol. 2, p. 482.
19. J.A. Berson and E. Brown, J. Am. Chem. Soc. (1955), 77, 444.
20. K.L. Marsi and K. Torre, J. Org. Chem. (1964), 29, 3102.
21. B. Singh and G.Y. Lesher, J. Heterocyclic Chem. (1980), 5, 1109.
22. A.R. Katritzky, T.I. Yousaf and D.L. Ostercamp, Tetrahedron, (1986), 42, 5729.
23. A.R. Katritzky and T.I. Yousaf, Canad. J. Chem. (1986), 64, 2087.
24. S.I. Selivanov, R.A. Bogatkin and B.A. Ershov, Zh. Org. Chem., (a) 17, (1981) 886; (b) 18, (1982) 909, (c) S.I. Selivanov, K.G. Goldova, Ya.A. Abbasov and B.A. Ershov, 20, (1984) 1494.
25. M. Cocivera and K.W. Woo, J. Am. Chem. Soc. (1976), 98, 7366.
26. L. Claisen; Zedal, W. Ber. 1891, 24, 140.
27. A. Hantzsch, ibid. 1891, 24, 495.
28. R. Uhlenhuth, Liebigs Ann. 1897, 296, 33.
29. A. Haller; E. Bauer, Compt. Rend. 1911, 152, 1446; (Chem. Abstr., 1911, 5, 3408).
30. R. Jacquier; C. Petrus; F. Petrus; J. Verducci, Bull. Soc. Chem. Fr. 1970, 2685.
31. N. Jacobsen; H. Kolind-Anderson; J. Christensen, Can. J. Chem. 1984, 62, 1940.
32. M. Cocivera; A. Effio; H.E. Chen; L. Vaish, J. Am. Chem. Soc. 1976, 98, 7362.
33. A.J. Boulton; A.R. Katritzky; A.M. Hamid; S. Øksne, Tetrahedron, 1964, 20, 2835.
34. M. Cocivera; K.W. Woo; P. Livant, Can. J. Chem., 1978, 56, 473.
35. A.R. Katritzky; P. Barczynski; D.L. Ostercamp, J. Chem. Soc. Perkin Trans. II, in press.