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THE MECHANISM OF THE HANTZSCH PYRIDINE SYNTHESIS: A STUDY BY ^{15}N AND ^{13}C NMR SPECTROSCOPY+

Alan R. Katritzky*, Daryl L. Ostercamp, and Taher I. Yousaf
Department of Chemistry, University of Florida,
Gainesville, FL 32611, USA

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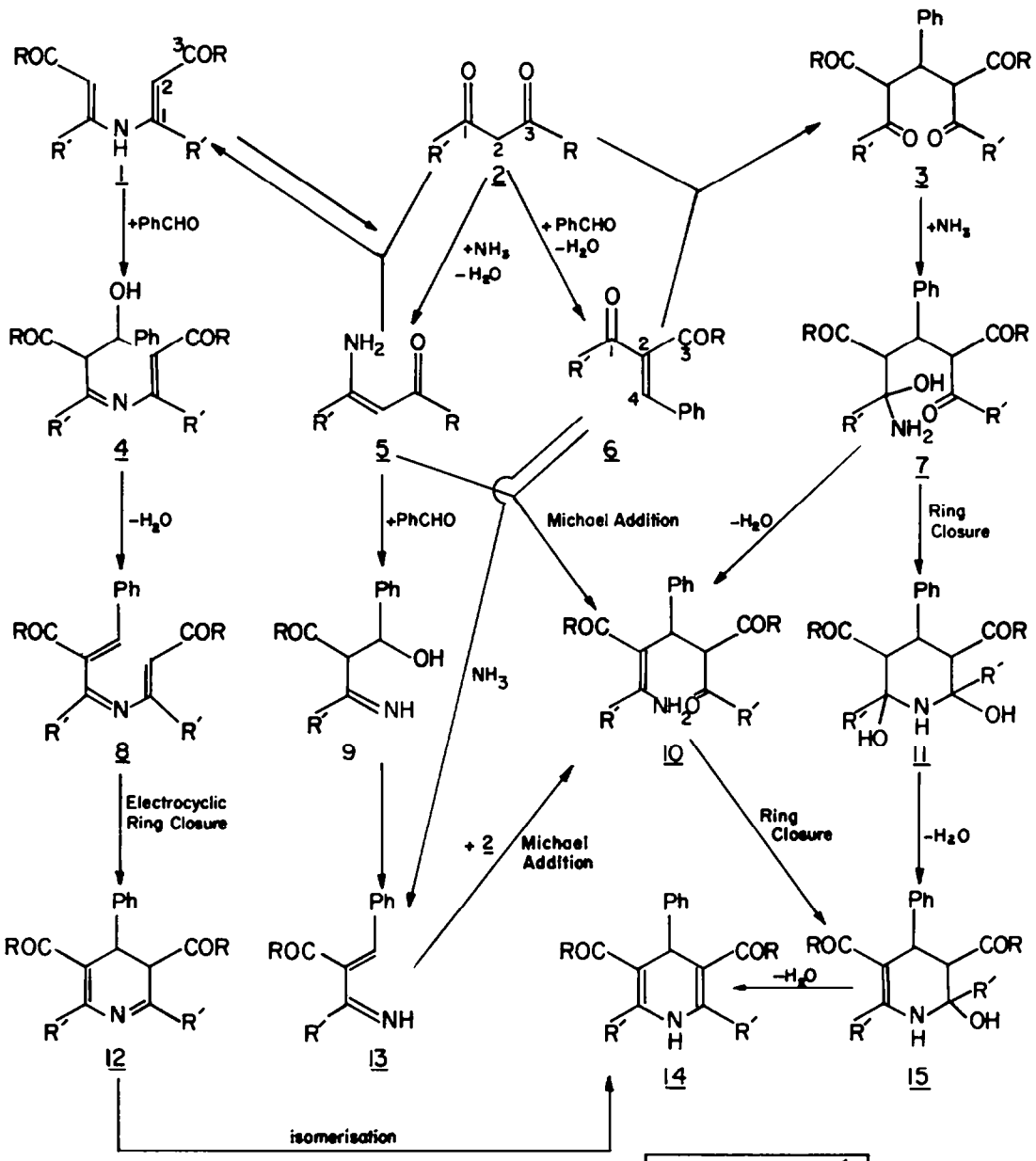
Abstract. The mechanism of the reactions of ammonia and benzaldehyde with three different beta-dicarbonyl compounds to form the corresponding dihyropyridines has been followed by NMR. In each case the pathway is shown to involve the reaction of benzaldehyde with one molecule of beta-dicarbonyl to give chalcone, and of the ammonia with a second molecule of beta-dicarbonyl to give an enamine. The rate determining stage is shown to be the Michael addition of the chalcone to the enamine.

The oldest, and perhaps most important, of the classical syntheses of pyridines is the reaction of a 1,3-dicarbonyl compound with an aldehyde and ammonia (or a primary amine), the Hantzsch (dihydro) pyridine synthesis.[1] This reaction has generally been assumed to proceed either via the intermediacy of an aminocrotonate 5 and an alpha, beta-unsaturated ketone 6 or via a 1,5-diketone 3.[2] In fact, as is shown in Scheme 1, the four components could join up in the final stage in a single 2 + 2 manner (i: 5 + 6 --> 10), or in one of three alternative 3 + 1 combinations (ii: 3 + NH_3 --> 7; iii: 1 + PhCHO --> 4; iv: 2 + 13 --> 10).

In the exceptional case of the reaction of 4,4,4-trifluoroacetoacetate 2d (Scheme 1) with a range of substituted benzaldehyes, the diols of type 11d have been isolated.[3,4] The isolation of only this diol in high yields implies that in this case: (i) the reaction proceeds exclusively via the 1,5-diketone 3d (Scheme 1) and not via the enamine 5d; (ii) ring closure of the carbinolamine 7d is faster than the elimination 7d --> 10d; (iii) the dehydration of 11d-->15d does not occur, even in the presence of strong dehydrating agents.[3] This type of mechanism parallels the reactions of 1,3-diketones with hydroxylamine[5], hydrazines[6], and amidines[7], all of which show heterocyclic diols as key reaction intermediates on the pathways to product.

With the important exception of 11d, apparently no intermediates have either been isolated or spectroscopically characterized in the Hantzsch pyridine synthesis[8]. Consequently, the older[8,9,10] and more recent[2] monographs on pyridine do not discuss in any detail the pathways delineated in Scheme 1, although some authors favor a particular mechanistic route: e.g., Mosher[9] cites the extensive earlier work on the effect of pH[11,12] and substituents[13] (in the benzaldehyde ring) on reaction yields, and favors the 1,5-diketone 3 pathway, whereas Berson[14], who made a number of 1,4-dihydropyridines, favours the aminocrotonate 5 pathway, simply on the basis of product composition.

+ This paper is considered as Part 3 of a series "The Mechanism of Heterocyclic Ring Closures. For parts 1 and 2 see references 7 and 15.



Scheme 1.

Reaction Pathways for the Hantzsch Synthesis of 1,4-Dihydropyridines

Series:	R	R′
a,	Me	Me
b,	OMe	Me
c,	Ph	Me
d,	OEt	CF_3

Scheme 1. Reaction Pathways for the Hantzsch Synthesis of Pyridines;

(i) enamine 5 + chalcone 6 --> 10 --> 15 --> 14

(ii) diketone 3 + NH_3 --> 7 --> (10 or 11) --> 15 --> 14

(iii) dienamine 1 + PhCHO --> 4 --> 8 --> 12 --> 14

(iv) enamine 5 + PhCHO --> 9 --> 13 + dicarbonyl 2 --> 10 --> 15 --> 14

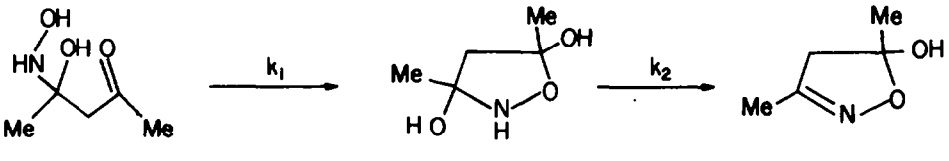
The present work was initiated to see if intermediates could be detected in the reactions of a variety of 1,3-dicarbonyl compounds (Table 1) with ammonia and benzaldehyde on the pathway to product 14 (Scheme 1). It is a continuation of our studies of heterocyclic ring closures by multinuclear NMR methods.[7,15,16] We have studied the reactions of benzaldehyde and ammonia with three beta-dicarbonyl components: methyl acetoacetate, acetylacetone, and benzoylacetone. The reactions were followed by ^{13}C, and ^{15}N NMR spectroscopy. We first discuss the mechanistic conclusions based on the intermediates detected, and then the spectral identification of these intermediates.

DISCUSSION

We observe that both the chalcone 6 and that the enamine 5 are always formed. The enamine is seen within minutes of the addition of ammonia and persists throughout the course of the reaction. This implies that the bulk of the reaction goes via the pathway of 5-->10-->15-->14. Peaks due to the chalcone 6 begin appearing within the first few hours of the reaction, gradually grow to a maximum, and, like the enamine 5 peaks, persist throughout the course of the reaction.

In two instances, direct combination of preformed compounds 5 and 6 (Et_3N catalyst) was shown to lead cleanly to the respective dihydropyridines 14a and 14b, at a rate somewhat slower compared to that found when using the usual starting materials. Because there is no reaction between benzaldehyde and either acetylacetone 2a or enamine 5a (Et_3N catalyst) after one week, we assume that formation of chalcones 6 involves the imine PhCH=NH[17] as an intermediate. In the presence of aqueous ammonia, compound 6a undergoes partial reversion to benzaldehyde and diketone 2a, and within a week significant amounts of enamine 5a and dihydropyridine 14a are formed from 6a. The absence of detectable quantities of the intermediates 10 and 15 (Scheme 1) implies that the ring closure 10 to 15 and the subsequent elimination 15 to 14 are faster than the Michael addition of 5 to 6.

If elimination from the diol 11 (Scheme 1) was faster than the ring closure 7 to 11, then the diol 11 would be present only in steady-state concentration and would therefore escape detection; furthermore, if formation of the carbinolamine 7 were faster than the Michael addition of 2 to the chalcone 6, no intermediates would be observed on the pathway 2-->3-->11-->14 other than the chalcone 6. This mechanism however, is implausible on the grounds that whenever diols lie on the pathway to products in heterocyclic ring closures, elimination from the diol has been shown to be slower than diol formation[5,6,7]; e.g., the rate of elimination from the diol 17 is ca. 10^6 slower than the rate of diol formation at pH 8.0.[5] Thus, if the diol 11 was an intermediate on the reaction pathway, it would be expected to gradually accumulate, and persist throughout the course of the reaction; as this is not the case, we conclude that the above pathway does not make a significant contribution to the mechanism of the Hantzsch pyridine synthesis.



16 17 18

$$\frac{k_1}{k_2} \sim 10^6$$

Table 1. C-13 NMR chemical shifts[a] and assignments of the beta-diketones 2a and 2c and beta-ketoester 2b (Scheme 1)

		C-1	C-2	C-3	R	R'	Literature
2a	keto	205.3	58.6	205.3	31.2 (Me)	31.2 (Me)	19a
	enol	192.8	101.4	192.8	25.1 (Me)	25.1 (Me)	
2b	keto	201.6	49.9	168.3	52.2(OMe)	30.0(Me)	19b
	enol	b	88.0	b	50.3(OMe)	21.0(Me)	
2c	keto	203.7	53.5	195.1		30.5(Me)	19c
	enol	194.0	96.7	182.6		25.3(Me)	

[a]In ppm relative to CD_3CN at 1.3 ppm. [b]Concentration of enol form too low to detect sp^2 carbons.

The dienamine species 1 is observable during the initial stage of the reactions involving aliphatic compounds 2a and 2b, respectively, but it could not be detected in the case of aromatic beta-diketone 2c. One hour after acetylacetone 2a, benzaldehyde, and ammonia are mixed, enamine 5a, chalcone 6a, and dienamine 1a are all present, but 1a disappears permanently before product 14a appears at the 24 hr mark. Early formation of enamine 5b and chalcone 6b from beta-ketoester 2b is also evident, with dienamine 1b and dihydropyridine 14b now emerging together at the six hour mark. Species 1b still remains after one day, but not after three days; after one day substantial conversion of reactants to product 14b has occurred. Approximately ten days are required before the combination of 2a with benzaldehyde and ammonia reaches a comparable stage of product (14a) formation. Since each of the dienamines 1a and 1b is outlasted by the related beta-dicarbonyl 2, enamine 5, and chalcone 6, we therefore conclude that 1a and 1b are metastable sideproducts, rather than intermediates in the conversion of 2 to 14.

Table 2. C-13 NMR chemical shifts[a] and assignments of the dihydropyridines 14(a-c) (Scheme 1)

	R	R'	C(2,6)	C(3,5)	(3,5 C=O)	C-4	Ph	R	R'	Literature
14a	Me	Me	144.8	114.5	(198.5)	41.2	b	30.5	19.7	21
14b	OMe	Me	145.6	101.6	(167.3)	40.3	c	51.4	19.0	21
14c	Ph	Me	142.5	111.3	(196.7)	42.6	d	e	18.3	--

[a]In ppm relative to CD_3CN at 1.3ppm. [b]Ph: o-129.5, m-128.6, p-127.4, i-148.4: ortho and meta assignments are interchangeable. [c]Ph: o-128.2, m-127.7, p-126.3, i-148.3: ortho and meta assignments are interchangeable. [d]Ph: o-126.7, m-127.8, p-126.0, i-146.5; ortho and meta assignments are interchangeable. [e]Ph: o-128.5, m-127.3, p-131.2, i 140.8; ortho and meta assignments are interchangeable.

Finally, we note that the 1,5-diketones 3a and 3b exist under our conditions as 3-hydroxycyclohexanone structures. Thus the original suggestion by Rabe and Elze[18] regarding ring-chain tautomerism for 3 is confirmed. Formation of 18a (R = R' = Me) from acetylacetone 2a and chalcone 6a (Et_3N catalyst) is complete within 4-8 hr.

SPECTRAL ASSIGNMENTS

C-13 NMR Assignments.

Table 1 gives the C-13 NMR chemical shifts and assignments of the 1,3-dicarbonyl compounds used in the present study. All are in good agreement with the literature references[19a-c] quoted in Table 1. Table 2 gives the C-13 NMR chemical shifts and assignments of the 1,4-dihydropyridines 14(a-c) (Scheme 1) formed from the reactions of the above 1,3-dicarbonyl compounds with ammonia and benzaldehyde. The ^{13}C NMR literature on 1,4-dihydropyridines is surprisingly sparse[20,21]; apparently spectra of only two of our compounds, 14a and 14b, have been previously reported.[21] Our values for these compounds (Table 2) are in excellent agreement with the literature. The two most characteristic carbons are the enamine type C(2,6) and C(3,4), both of which resonate within the expected regions[22a]: ca. 135-155 ppm and ca. 90-120ppm, respectively. Little change occurs in the chemical shift of the acyl carbonyl (C-3) of the beta-ketoester 2b in going from starting material (Table 1) to product 14b (Table 2). The corresponding carbons in the starting beta-diketones 2a and 2c are shifted upfield by ca. 6ppm in the products 14a and 14c (Table 2), due to conjugation with the enamine double bond. Little change occurs (less than 2ppm) in the chemical shifts of the R-substituents in going from starting materials 2(a-c) (Table 1) to products 14(a-c) (Table 2), as they are isolated from the enamine double bond. The product methyls (Table 2, R') resonate at ca. 18-20 ppm, within the region expected of an sp^3 carbon attached to a double bond.[23a] By contrast, the methine carbons (C-4) of products 14(a-c) resonate ca. 20ppm downfield of these methyls (Table 2) as each is attached to three sp^2 carbon atoms.[24a] An upfield shift of the benzaldehyde ring carbons occurs in the products 14(a-c) (Table 2); the shift is small (ca. 1-2ppm) for the ortho- and meta- carbons but somewhat larger (ca. 10 ppm) for the para- carbons. The cause is the methine carbon (C-4) of product which is weakly electron releasing (through hyperconjugation of the hydrogen with the phenyl ring). In confirmation, the ipso-carbons of products 14(a-c) (Table 2) are ca. 10ppm downfield of the ipso-carbon in benzaldyde (137.0 ppm).

Table 3. C-13 NMR chemical shifts[a] and assignments of the intermediates 5(a-c) (Scheme 1)

	R	R'	C-1	C-2	C-3	Literature
5a	(Me) 29.1	(Me)22.2	165.1	95.8	197.1	19d
5b	(OMe)50.3	(Me)21.9	162.8	82.3	171.2	---
5c	(Ph[b])	(Me)21.7	164.5	90.5	186.7	---

[a]In ppm relative to CD_3CN at 1.3ppm. [b]Phenyl: o-128.1, m-126.6, p-130.4, i-140.2; ortho and meta assignments are interchangeable.

Table 4. C-13 NMR chemical shifts [a] and assignments of the intermediates 6(a-c) (Scheme 1)

	C-1	C-2	C-3	C-4	R	R'	Ph	Literature
6a	206.1	143.8	198.2	140.6	26.7	32.1	b	19e
6b(Z)-	203.8	135.0	165.7	141.2	53.1	31.7	c	---
6b(E)-	196.4	135.0	169.0	142.4	53.1	26.6	d	---
6c(E)[e]-	197.9[f]	139.7	197.6[f]	142.0	(Ph[g])	26.3	h	---

[a] In ppm relative to CD_3CN at 1.3 ppm. [b] Phenyl: o-130.7, m-129.9, p-131.4, i-134.1: ortho- and meta- assignments are interchangeable. [c] Phenyl: o-130.7, m-130.1, p-131.5, i-134.1; ortho- and meta- assignments are interchangeable. [d] Phenyl: o-130.5, m-130.1, p-131.8; i-134.1; ortho- and meta- assignments are interchangeable. [e] only one stereoisomer was isolated. [f] Interchangeable. [g] Phenyl: o - 129.9, m- 128.8; p- 134.1, i-135.8; ortho- and meta- assignments are interchangeable [h] Phenyl o-129.1, m- 128.6, p- 130.4, i- 132.9; ortho and meta- assignments are interchangeable.

Tables 3 and 4 give the chemical shifts and assignments of the enamines 5(a-c) and chalcones 6(a-c) detected as intermediates in these reactions. The two key enamine carbons C-1 and C-2 (Table 3) resonate in the region expected for an enamine conjugated with a carbonyl carbon.[22a,25] The same conjugation decreases the chemical shifts of C-3 in the enamines 5a and 5c (Table 3) by ca. 8-10ppm from that of C-3 in the corresponding beta-diketones 2a and 2c (Table 1), but makes little difference to the chemical shift of the acyl carbonyl C-3 in the enamine 5b (Table 3). Although the enamines 5(a-c) may be formed as mixtures of the (E)- and (Z)-isomers, only the (Z)-isomer is observed[26] presumably because it is stabilised by intramolecular hydrogen bonding between the enamine hydrogen and the carbonyl oxygen. By contrast, the chalcone 6b (Table 4) is formed as a mixture of isomers, with the (E)-form predominating [(E)/(Z)ca. 5/1 as obtained from C-13 NMR peak heights].

Trends in the chemical shift differences of the chalcones 6(a-c) (Table 4) may also be analysed by the above procedure, and in fact, the chemical shifts of the main carbon skeleton C-1, C-2, C-4 in the chalcones 6(a-c) (Table 4) parallel those of other enone systems reported in the literature.[23b,24b]

Changes in the chemical shifts of the carbonyls C-1 and C-3 and the substituents R and R' in going from starting materials 2 (a-c) (Table 1) to the chalcones 6 (a-c) (Table 4) are reasonably ascribed to steric effects,[23c] those atoms SYN to the phenyl being shielded and those ANTI being deshielded.

Peaks that might correspond to the diol 11 were never observed. Of these, the most characteristic should be that due to the quaternary carbons C(2,6), expected in the region 80-100ppm[22b,27] and previously observed by us in other dihydroxy intermediates.[7] No additional peaks were observed in this region even upon using very long pulse delays (cf. Experimental) to enhance the quaternary carbons.

The dienamine 1 (Scheme 1) was identified in the early stages of the reaction in two instances (see above); chemical shifts and assignments of structures 1a and 1b, respectively, are collected in Table 5. Only minor differences are noted between the peak positions for carbonyl carbon and the two methyl substituents (R and R') of dienamine 1a (Table 5) and those of enamine 5a (Table 3) and dihydropyridine 14a (Table 2). Cross-conjugation of the nitrogen atom affects significantly the enamine core carbon atoms of both 1a and 14a. In the dienamine 1a the chemical shifts of C-1 and C-2 decrease by ca. 18 ppm and increase by ca. 12 ppm, respectively, from those of C-1 and C-2 in reference enamine 5a; analogous changes are noted within the C-13 NMR spectrum of product 14a. In similar fashion one may also correlate peak positions with structure for metastable sideproduct 1b (Table 5), intermediate 5b (Table 3), and product 14b (Table 2).

Spectral evidence supporting cyclohexanone structure 18 as the favored (ring) tautomer of 1,5-diketones 3a and 3b is assembled in Table 6. Use of INEPT (D) pulse sequences[15] readily identified the ring methylene C-1, this technique also confirmed that methine C-4 was associated with a signal at ca. 46 ppm, a shift value comparable to that of C-4 in product 14 (Table 2). Additional consistency in signal locations of C-6 and its attached methyl group is also evident in Table 6. The chemical shifts of the tertiary (ether) carbon and its (identical) methyl substituent(s) of the methyl ether of diacetone alcohol[19e] are 74.1 ppm and 24.9 ppm, respectively. In completing the assignments in Table 6, we note in particular the changes in keto carbon (C-1) signals of 205.3 ppm to 201.6 ppm and of methylene (C-2) signals 58.6 ppm to 49.9 ppm proceeding from acetylacetone 2a to methyl acetoacetate 2b, respectively. Differences between C-3' and C-5' carbonyls in 18a and 18b and between 3'-Me and 5'-Me in 18a are ascribed to steric effects.[23c]

Table 5. C-13 NMR chemical shifts[a] and assignments of dienamines 1(a-b) (Scheme 1)

	R	R'	C-1	C-2	C-3
1a	(Me)30.2	(Me)22.6	145.5	108.5	196.3
1b	(OMe)50.7	(Me)19.7	145.9	94.0	171.5

[a] In ppm relative to CD_3CN at 1.3 ppm.

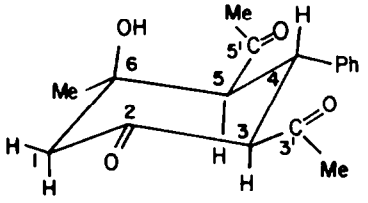
N-15 NMR Assignments

The chemical shift of nitrogen is very sensitive to the degree of hybridisation of the nitrogen.[28a] Pure sp^3 nitrogens resonate ca. 300 to 500 ppm upfield of nitromethane[28a] (e.g. NH_3 in our medium comes at -466.3 ppm) whereas pure sp^2 nitrogens resonate in the downfield region at ca. 100 to -100 ppm (N=C)[28a] and 500 to -50 ppm (N=O).[28b] In the reaction of 1-3,dicarbonyl compounds 2a and 2b with ammonia and benzaldehyde (Scheme 1), N-15 NMR signals were observed at -277.0 ppm for intermediate 5b, and also at -241.3 ppm for dihydropyridine 14a and -246.3 ppm for dihydropyridine 14b. All the chemical shifts are within the region expected for an enamine type nitrogen (-200 to -300 ppm),[28b,29] but the chemical shifts of products 14a and 14b are 30-40 ppm downfield of the intermediate 5b (Table 5). The small downfield shift of the product 14a and 14b nitrogens relative to the intermediate 5b may therefore be rationalized in terms of an increase in sp^2 character of the product nitrogen due to cross-conjugation with two double bonds. The absence of peaks in the pure sp^2 region rules out the possibility of imines as intermediates on the reaction pathway, and similarly, the absence of additional peaks in the sp^3 region rules out the diol 11 (Scheme 2).

Table 6. C-13 NMR Chemical Shifts[a] and Assignments for Structure 18.

Compd	C-1	C-2	C-3	C-4	C-5	C-6	C-3'	C-5'	3'-R	5'-R	Me	Ph
a	55.0	206.2	68.3	46.3	62.4	74.9	206.2	205.6	34.0	31.6	28.8	b
b	54.1	203.6	63.3	46.2	57.7	74.2	174.1	169.9	52.3	52.3	26.8	c

[a]In ppm relative to CD_3CN at 1.3 ppm. [b]Ph: o-129.9, m-129.3, p-128.6, i-140.7; ortho and meta are interchangeable. [c]Ph: o-129.9, m-129.1, p-128.7, i-140.5; ortho and meta are interchangeable.



18 a

CONCLUSIONS

The detection of intermediate chalcones 6 as well as intermediate enamines 5 in all reactions studied, together with the demonstration that preformed chalcones and enamines form the dihydropyridine indicates clearly that the Hantszch dihydropyridine synthesis usually occurs by pathway (i) of Scheme 1. The lack of observation of other intermediates supports this interpretation.

EXPERIMENTAL

All reagents were obtained from Aldrich, characterized by their ^{13}C-NMR spectra (Table 1), and used without further purification. Melting points were determined on a Kofler hot-stage and are uncorrected. Elemental analyses were carried out in the department on a Carlo-Erba Elemental Analyser 1106.

General Method.

Reactions were carried out in NMR tubes and followed in the spectrometer cavity by observing the decay of peaks due to starting materials, the growth and gradual decay of peaks due to intermediates, and the concomitant formation of product peaks; these peaks were characterized by comparison with spectra of authentic samples of products made by literature methods. Starting material and intermediate peaks were assigned by reference (where possible) to literature values and by the use of two INEPT(D) pulse sequences[15].

Reactions followed by ^{13}C-NMR were started by the addition of ca. 0.001 mole of NH_3 aq. (as a 28% v/v solution) from a hypodermic syringe into a 5 mm NMR tube containing beta-ketoester or beta-diketone (0.002 mole) and benzaldehyde (0.001 mole), and sufficient CD_3CN to make the total volume to ca. 0.5 ml. The initial concentration of reagents was therefore ca. 2 mol L^{-1}. These high initial concentrations are necessary if the reaction intermediates are to be seen clearly. Reactions involving the preformed intermediates, the chalcones 6 and the enamines 5, were also carried out by a similar procedure, a drop of triethylamine being added to each run.

Reactions followed by ^{15}N-NMR were carried out in 12mm NMR tubes using ca. 0.1 mole of starting materials, with CH_3NO_2 as external reference and DMSO-d^6 as solvent, making the total volume up to ca. 3 ml. These large volumes were necessary because the N-15 NMR spectra were taken at natural abundance.

Spectra.

All spectra were taken at ambient probe temperatures (ca. 22-25°C). C-13 NMR spectra were taken on a JEOL FX-100 spectrometer at 25.1 MHz with a 6kHz sweep width and 8K data points using a 19 micro second (90°) pulse width, 2 second pulse delay and ca. 0.68 second aquisition time; this afforded a digital resolution greater than 1.5 Hz per point. Longer delays (ca. 6 seconds) were also employed to enhance peaks due to the quaternary carbons of the intermediates 5 and 6, and the product, 14. Accumulations varied from 10^3-10^4 for each spectrum, giving signal:noise ratios > 10^2:1.

Spectra were taken immediately upon mixing, and at intervals of ca. 1-3 hrs for the initial 24 hr. Attempts to speed up the reaction by increasing the cavity temperature up to the range 45-55°C gave product peaks within minutes and disclosed no intermediate peaks.

N-15 NMR spectra were takes at natural abundance on a Nicolet NT 300 at 30.4 MHz using a 24 micro second (65.5°) pulse width, 6 second pulse delay and 0.82 second aquistion time. The digital resolution was 1.2 Hz per point using a 20kHz sweep width with 32K data points; ca. 10^4 accumulations were taken for each spectrum, giving a signal:noise ratio > 10:1. DMSO-d_6 was used as internal lock and CH_3NO_2 as external standard.

Synthesis.

The following compounds were made by the literature methods cited: benzylidenebisacetylacetone 3a, m.p. 165-166° (72%) (reported[13e] 166°) ^{1}H NMR ($CDCl_3$) delta 1.32(s, 3H, 6-CH_3), 1.68(s, 3H, 5'-CH_3), 2.06(s, 3H, 3'-CH_3), 2.56(d, J=14 Hz, 1H, H-1), 2.66(d, J=14 Hz, 1H, H-1), 3.31(d, J= 12 Hz, 1H, H-5), 3.88(t, J=12 Hz, H-4), 4.00(s, 1H, OH), 4.03(d, J=12 Hz, 1H, H-3), 7.31(m, 5H, Ph); dimethyl benzylidenebisacetoacetate 3b, m.p. 186-188° (62%) (reported[30] 183°); 4-amino-3-penten-2-one 5a, m.p. 42-43° (61%) (reported[31] 43°); methyl beta-aminocrotonate 5b, m.p. 81-82° (80%) (reported[32]85°); 3-amino-1-phenyl-2-buten-1-one 5c, m.p. 144-145° (85%) (reported [13c] 143°); benzylideneacetylacetone 6a, b.p. 118-120°/0.5 mm. (68%) (reported[33] 179-181°/12 mm); methyl benzylideneacetoacetate 6b, b.p. 85-88°/0.2 mm (28%) (reported[34] 158-162°/12mm); benzylidenebenyoylacetone 6c, mp 100-101° (69%) (reported[35] 98-99°); 2,6-dimethyl-3,5-diacetyl-4-phenyl-1,4-dihydropyridine 14a, m.p. 180-182° (86%) (reported[13d] 180°; calcd.: C, 75.8, H, 7.1, N, 5.2; found: C, 75.6, H, 7.3, N, 5.0); 2,6-dimethyl-3,5-dicarbomethoxy-4-phenyl-1,4-dihydropyridine 14b, m.p. 196-198° (91%) (reported[36] 197-198°; calcd.: C, 67.8, H, 6.4, N, 4.7; found: C, 67.4, H, 6.5, N, 4.4), 2,6-dimethyl-3,5-dibenzoyl-4-phenyl-1,4-dihydropyridine 14c, m.p. 226-228° (37%) (reported[13c] 222°). Chalcones 6a and 6c were prepared by the method of Pratt and Werble.[37]

REFERENCES

1. Hantzsch, A. Ann. 1882, 215, 1.
2. Jones, G. In 'Comprehensive Heterocyclic Chemistry'; Katritzky, A.R., Rees, C.W. Eds.; Pergamon Press: Oxford, 1984; Volume 2, p482.
3. Singh, B., Lesher, G.Y. J. Heterocyclic Chem. 1980, 17, 1109.
4. Balicki, R., Nantka-Namirski, P. Acta Pol. Pharm. 1974, 31, 261. Chem. Abs. 1975, 82, 72739p.

5. Cocivera, M.; Woo, K.W. J. Am. Chem. Soc. 1976, 98, 7366.
6. (a) Selivanov, S.I.; Bogatkin, R.A.; Ershov, B.A. J. Org. Chem.(USSR), 1981, 17, 780. (b) Selivanov, I.; Bogatkin, R.A.; Ershov, B.A. Ibid. 1982, 18, 788. (c) Selivanov, S.I.; Golodova, K.G.; Abbasov, Ya. A.; Ershov, B.A. Ibid. 1984, 20, 1361.
7. Katritzky, A.R.; Yousaf, T.I.; Can. J. Chem., in press.
8. Smith, D.M. In "Rodd's Chemistry of Carbon Compounds'; Coffey, S., Ed.; Elsevier: Amsterdam, 2nd ed., 1976; Volume 4F, p 34ff.
9. Mosher, H.S. In 'Heterocyclic Compounds'; Elderfield, R. Ed., Wiley: New York, 1950; Volume 1, p 397 ff.
10. Brody, C., Ruby, P.R. In 'Pyridine and its Derivatives, Part 1; Weissberger, A., Ed.; Interscience: New York, 1960, p 500f
11. (a) Hinkel, L.E.; Ayling, E.E.; Morgan, W.H. J. Chem Soc. 1931, 1835. (b) Hinkel, L.E.; Ayling, E.E.; Morgan, W.H. Ibid. 1935, 816.
12. Haley, C.A.C.; Maitland, P. Ibid. 1951, 3155.
13. Knoevenagel, E. (a) Ann. 1895, 288, 321. (b) Ber. 1898, 31, 738. (c) Ibid. 1903, 36, 2180. (d) Knoevenagel E.; Ruschhaupt, W. Ibid. 1898, 31, 1025. (e) Knoevenagel, E., Werney, R. Ann. 1894, 281, 79.
14. Berson, J.A.; Brown, E. J. Am. Chem. Soc. 1955, 77, 444.
15. Katritzky, A.R.; Yousaf, T.I.; Chen, B.C.; Zeng, G.Z. Tetrahedron, 1986, 42, 623.
16. Katritzky, A.R.; Barczynski, P.; Yousaf, T.I.; Ostercamp, D.L. J. Org. Chem. submitted.
17. Carey, F.A.; Sundberg, R.J.; "Advanced Organic Chemistry. Part B: Reactions and Synthesis", 2nd ed., Plenum Press, N.Y. 1984, p 57.
18. Rabe, P. and Elze, F.; Ann., 1902, 323, 83.
19. The Sadtler Standard Carbon-13 NMR Spectra: (a) Spectrum 914; (b) Spectrum 1611; (c) Spectrum 868; (d) Spectrum 5245; (e) Spectrum 2266; (f) Spectrum 2305.
20. Dommisse, R.A.; Lepoivre, J.A.; Alderweireldt, F.C.; Bull. Soc. Chim. Belg. 1977, 86, 267.
21. Kurfurst, A; Trska, P.; Goljer,I; Coll. Czech. Chem. Comm., 1984, 49, 2393.
22. Shamma, M.; Hindenlang, D.M.; "Carbon-13 NMR Shift Assignments of Amines and Alkaloids"; Plenum Press New York, 1979; (a) pp 47-54; (b) pp 261-287.
23. Levy, G.C.; Lichter, R.L.; Nelson, G.L. "Carbon-13 Nuclear Magnetic Resonance Spectroscopy"; Wiley: New York, 2nd ed., 1980; (a) p 78; (b) p 141; (c) p 55.
24. Silverstein, R.M.; Bassler, G.C.; Morrill, T.C.; "Spectrometric Identification of Organic Compounds"; John Wiley: New York, 1981; (a) p 261; (b) p 264.
25. Dabrowski, J.; Kamienska-Trela, K.; Kozerski, L. Org. Mag. Resonance 1974, 6, 499.
26. Marsi, K.L.; Torre, K. J. Org. Chem. 1964, 29, 3102.
27. Chudek,J.A.; Foster, R.; Young,D. J. Chem Soc. Perkin II, 1985, 1285.
28. Levy, G.C., Lichter, R.L. "Nitrogen-15 Nuclear Magnetic Resonance Spectroscopy"; Wiley: New York, 1979; (a) p 8 ff; (b) p 29.
29. Kozerski, L.; von Philipsborn, W. Org. Mag. Resonance, 1981, 17, 306.
30. Dieckmann, W. Ber. 1912, 45, 2689.
31. Combes, A.; Combes, C. Bull. Soc. Chem. Fr. 1892, III 7, 778.
32. Conrad, M.; Epstein, W. Ber. 1887, 20, 3052.
33. Knoevenagel, E.; Faber, W. Ber. 1898, 31, 2773.
34. Erickson, J.G. J. Am. Chem. Soc. 1945, 67, 1382.
35. Knoevenagel, E.; Erler, A. Ber., 1903, 36, 2131.
36. Phillips, A.P. J. Am. Chem. Soc. 1948, 71, 4003.
37. Pratt, E.F.; Werble, E. J. Am. Chem. Soc. 1950, 72, 4638.