# Enazine Chemistry II. The Mechanism of Formation of
1-(cis-3-Phenylpropenyl)-5-phenylpyrazole from the Pyrolysis of Cinnamaldehyde Azine (1).

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The mechanism of pyrazole formation from the thermolysis of α,β-unsaturated azines has been examined by both kinetic and non-kinetic methods. The reaction exhibits a large negative entropy of activation, a large primary isotope effect and a positive slope in a Hammett study on cinnamaldehyde derivatives. The reaction was shown to be cleanly intramolecular and was also unaffected by radical traps. A mechanism involving intramolecular 1-5 abstraction of a proton is presented, which accounts for all of the experimental data.

Three distinctly different thermal reactions of azines are now known. The first of these, observed with alda-zines, involves the loss of molecular nitrogen and generation of alkene product (*i.e.* benzaldehyde azine yields stilbene) (3). The mechanism of this latter reaction is now well established as an ionic chain process, in which the chain transfer agent is an aryldiazomethane (4a-b). A second reaction is observed when arylketazines are pyrolyzed. When benzophenone azine is heated to temperatures of 375-500°, major products of the reaction are benzhydrili-dine imine, benzonitrile and 6-phenylphenanthridine, accompanied by lesser amounts of a host of minor products (5). This reaction was shown to proceed via a free radical pathway. A third thermal reaction of azines was recently reported by Stern and Krause (1). This reaction involves the generation of *N*-propenylated pyrazoles from the thermolysis at 200° of certain α,β-unsaturated azines (see equation 1). The mechanism of this novel synthesis of a previously unreported type of pyrazole has remained obscure since it was first reported (6).

$$R_1 = H, CH_3, C_6H_5$$
$$R_2 = H, CH_3, C_6H_5$$
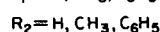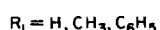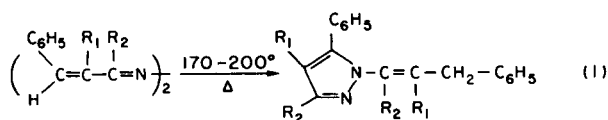
We wish to report here the results of an investigation of the mechanism of this reaction (equation 1), which has been carried out on the simplest system (*i.e.* $R_1 = R_2 = H$).

The pyrolysis of cinnamaldehyde azine was examined in 2-ethoxynaphthalene, a solvent which is susceptible to free radical and electrophilic attack (4), to determine whether the reaction represented by equation 1 is free radical in nature. The pyrolysis of azine in a twenty-five fold molar excess of 2-ethoxynaphthalene yielded only the normal pyrazole product, without inhibition. The conversion of azine to pyrazole was also found to be unaffected by the presence of molecular oxygen, a known free radical scavenger (7). These results imply that reaction 1 is in fact not a free radical process.

Next, an experiment was carried out to determine if the reaction was intra- or intermolecular. The conventional cross-over approach was employed. The required azine, *p*-methyl-α-phenylcinnamaldehyde azine (1) was prepared from *p*-tolualdehyde and phenylacetic acid as indicated in Figure 1. When this azine was pyrolyzed, an 85% yield of
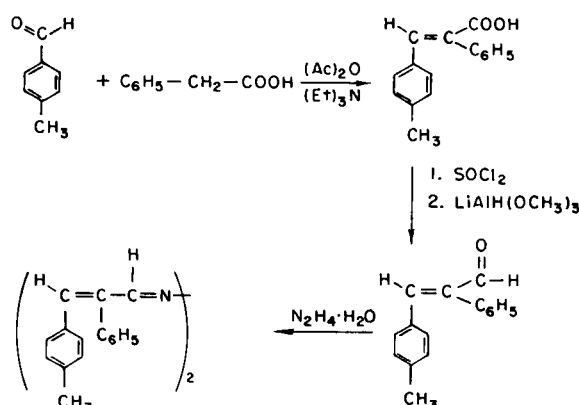
FIGURE 1

1. Synthesis of *p*-Methyl-α-phenylcinnamaldehyde Azine.

the expected pyrazole was obtained, assayed spectrophoto-metrically. An equimolar mixture of this azine (1) and cinnamaldehyde azine (2) were pyrolyzed. While the expected pyrazole compounds 3 and 4 were found, the cross-over products, pyrazoles 5 and 6 were conspicuous by their absence (see Figure 2). This experimental result demands that the reaction mechanism is intramolecular (8).
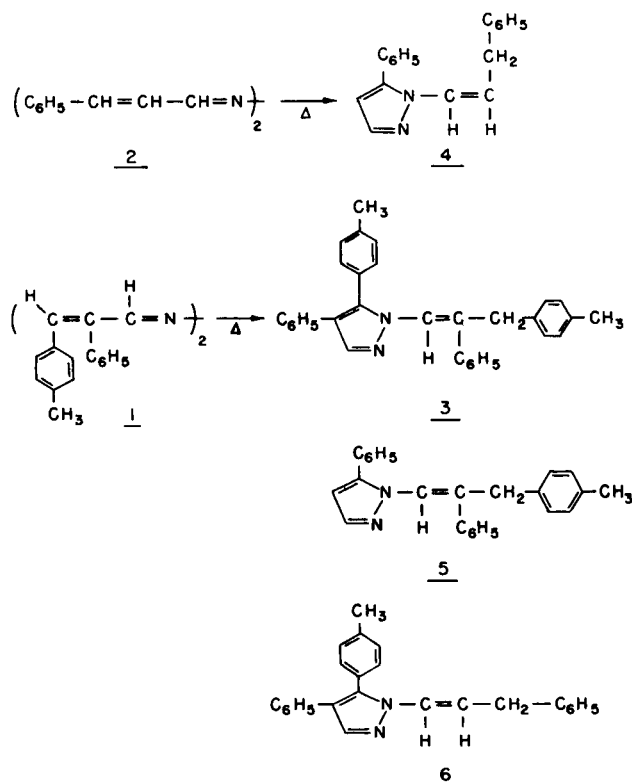

FIGURE 2

2. Cross-over Experiment to Test Intramolecularity of Pyrazole Formation.

While the reaction as a whole is, from the above result, intramolecular, it is possible that the migration of hydrogen (which is superficially a 1-8 shift) might in fact be an intermolecular stepwise process occurring with the concomitant intramolecular cyclization to pyrazole. This problem was resolved as follows: the β-deutero derivative of cinnamaldehyde azine (7) was synthesized, as indicated in Figure 3. This azine was pyrolyzed to the corresponding pyrazole, and careful quantitative examination of the proton nmr spectrum revealed that greater than 98% of the deuterium in the pyrazole was at the benzylic position indicated (see equation 2) of the pyrazole (8). Thus, it
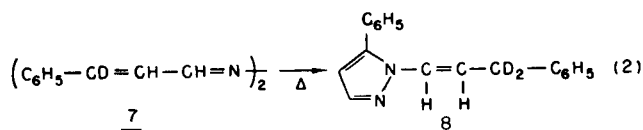
follows that the migration of hydrogen could not have taken place in a step wise fashion, since if it had, some deuterium would have been observed in vinylic positions, as well as at the benzylic position.

This result does not however rule out the possibility that the migration of hydrogen might still be inter-molecular. To test this possibility, the pyrolysis reaction was carried out in benzyl alcohol -O-D, a good source of deuterons, and in triphenylmethane-D which could supply D^- ions. If hydrogen (either as H^+ or H^-) was ever free of carbon, it might be anticipated that in these deuterated solvents deuterium would be incorporated into the pyrazole product. However, in both experiments, cinnam-aldehyde azine yielded 1-(cis-3-phenylpropenyl)-5-phenyl-pyrazole containing less than 2% deuterium. It is thus concluded that the migration of hydrogen takes place in a manner that precludes interception by solvent. It should be noted that the experimental result does not necessarily rule out the migration of hydrogen as a proton or hydride ion in an intramolecular sense.

The kinetics of cinnamaldehyde azine pyrolysis was conveniently determined using ultraviolet spectroscopy as the method of analysis. The absorption maxima of the reactant and product were easily discernable for all azines used, so that the rate of appearance of product as well as the rate of disappearance of reactant could be easily monitored. Excellent linear correlations resulted from plots of log a/a-x versus time, thereby establishing the reaction as a first order process (9). The data obtained in the kinetic study is summarized in Table I.

TABLE I

Tabulation of Rate Constants for the Pyrolysis of Several Cinnamaldehyde Azines at Various Temperatures (a)

Azine	Temperature (°C)	k (sec^{-1} x 10^3)
Cinnamaldehyde	180	1.12
	190	2.18
	200	4.32
β-Deuterocinnamaldehyde	200	1.64
p-Methylcinnamaldehyde	200	2.88
	210	5.34
p-Methoxycinnamaldehyde	200	2.58
p-Chlorocinnamaldehyde	220	29.6

(a) The rates were measured in triplicate at each temperature with an average deviation of 10% in the rate constants. Activation parameters and isotope effects were determined at 200° using conventional procedures (11).

From the rate constants determined at different temperatures, activation parameters could be calculated using conventional procedures (10). The enthalpy of activation, ΔH^*, and entropy of activation ΔS^*, were

found to be 26.8 ± 1.2 kcal/mole and -15.5 ± 1.0 e.u. respectively at 200°, and the frequency factor was 1.2 x 10¹⁰. The large negative entropy of activation, and the

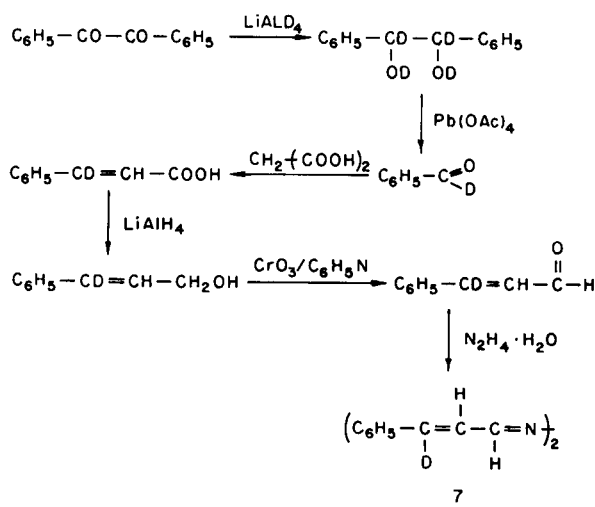FIGURE 3

3. Synthesis of β-Deuterocinnamaldehyde Azine.

magnitude of the frequency factor both imply strongly that the transition state is highly ordered with respect to ground state in the slow step of this reaction (11). In fact, one ordinarily associates entropies of activation of this size with cyclic transition states (12).

An interesting observation was the fact that the β-deutero derivatives of cinnamaldehyde azine underwent the pyrolysis reaction rather sluggishly at 200°. From the data in Table I it is possible to calculate an isotope effect k_H/k_D of 2.7, a value too large to be associated with a secondary isotope effect, but quite compatable with a primary isotope effect (13). In fact, k_H/k_D at 200° has a calculated maximum value of 3.2 (13). It can safely be concluded from this result that the rate determining step must involve the breaking of a C-H bond. In addition, since the maximum isotope effect corresponds to a situation in which bond breaking and bond making are very nearly equal (14), the implication is that in the pertinent transition state the migration of hydrogen atom is roughly mid-way between the carbon atoms that constitute the origin and terminus of the migration.

It would be of interest to know whether this hydrogen migration is that of a proton or of a hydride ion. The data in Table II was plotted to see if the Hammett relationship is obeyed. The relationship of these four values was found to be cleanly linear with a slope, ρ, equal to +1.06 in a plot of the log of the rate constant versus σ. The fact that rho is positive for this reaction implies that the migration terminus, the benzylic carbon atom of the

product, must have had carbanion character in the transition state of the slow step, since electron withdrawing substituents facilitate the reaction. Therefore, the hydrogen must migrate as a proton to this carbanion center.

In a previous publication (1) it was shown that neither β-methylcinnamaldehyde azine nor β-phenylcinnamaldehyde azine gave pyrazole products on pyrolysis, and in fact these azines were pyrolitically inert at temperatures up to 250°. Any mechanistic description must then account for this fact as well as the intramolecular migration of a proton in the slow step.

The following mechanism (Figure 4) is presented to account reasonably for all of the kinetic and non-kinetic data presented in the previous sections of this paper. The configuration of the starting azine is known to be all trans (14). It is known that above the melting point geometrical isomerization of imine double bonds occurs in this system (15). Thus formation of the isomerized azine (9) is reasonable, and electronic reorganization of compound 9 to the meso-ionic intermediate 10 finds analogy in the accepted mechanism for the 1-4 addition of hydrazine to α,β-unsaturated carbonyl compounds to yield pyrazolines (16). It should be noted that species 10 is an allylic anion. Such anions are believed to have as important tautomers cis anions such as 11 (17). The meso-ionic intermediate 11 has the carbanion center well within bonding distance of the benzylic hydrogen that is ultimately abstracted. The rate determining step is, we suggest, the proton abstraction and electronic reorganization of intermediate 11, leading to the pyrazole product.

The proposed mechanism is clearly consistent with the experiments carried out with radical trapping agents, and accounts for the negative results of the cross-over experiment. In addition, the specific 1-8 transfer of hydrogen is reasonably explained by this mechanism (which is as Figure 4 indicates in actuality a 1-5 proton migration). The kinetic results can all be accommodated. The
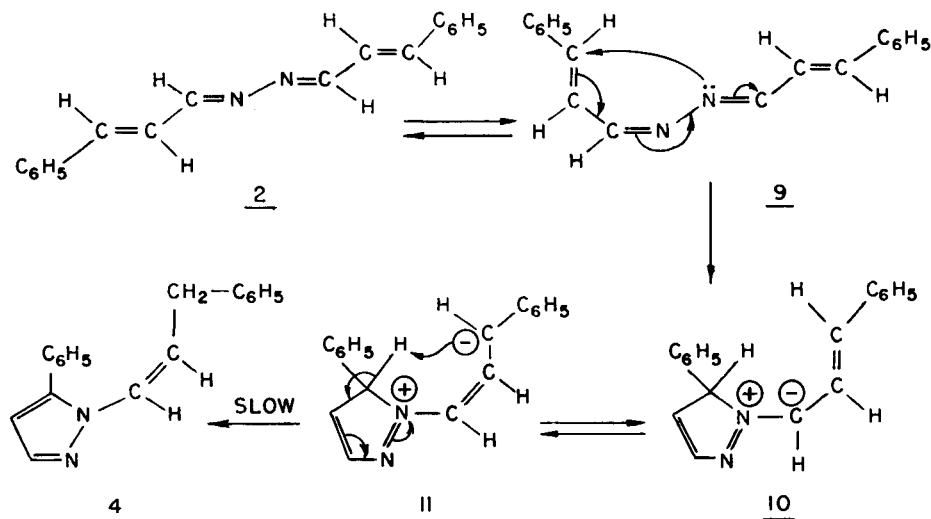
FIGURE 4

4. Proposed Mechanisms for the Thermal Generation of Pyrazole from Azine.

mechanism proposed will exhibit first order kinetics, and if the slow step is that indicated, will have associated with it a large negative entropy of activation. Also the positive sign of *rho* in the Hammett study is consistant with the abstraction of a proton by the allylic anion in intermediate **11**. Likewise the observed primary isotope effect would be expected in the slow step described in Fi gure 4.

One point appears to be inconsistent with the mechanistic description. Namely, the failure of benzyl alcohol O-D to introduct deuterium into the pyrazole, when it was employed as solvent. This apparent inconsistency can be understood by examining carefully the proton which is abstracted in the intermediate **11**. This proton is benzylic, and doubly allylic (once with respect to a quarternary nitrogen atom). On this basis it would be expected that this proton would be many orders of magnitude more acidic than the pertinent hydrogen atom in benzyl alcohol. Thus, it is clear that benzyl alcohol cannot compete with the afore-mentioned proton in the pyrazole precursor **11**.

EXPERIMENTAL (18)

Pyrolysis of Cinnamaldehyde Azine (**2**) in 2-Ethoxynaphthalene.

A mixture of azine (0.26 g., 1.0 mmole) and 2-ethoxynaphthalene (19) (3.4 g., 20 mmoles) was heated in an oil bath at 200° for 30 minutes. The mixture was cooled and eluted with benzene on a silica gel column. Early fractions contained 0.25 g. (96%) of 1-(cis-3-phenylpropenyl)-5-phenylpyrazole (**4**)

which was identified by the infrared spectrum and later fractions contained 3.4 g. (100%) of 2-ethoxynaphthalene, m.p. 34-36° (lit. 36-40° (4a).

Pyrolysis of Cinnamaldehyde Azine (**2**) in an Oxygen Atmosphere.

Azine (1.0 g. 4.0 mmoles) was placed in a test tube which was swept with oxygen for ten minutes. A gas dispersion tube was inserted into the bottom of the tube. The azine was melted in an oil bath at 200° and oxygen was bubbled through the melt for 30 minutes. Thin layer chromatography and infrared spectroscopy revealed that the product, compound **4**, was identical to that obtained when the pyrolysis was carried out under oxygen free conditions.

Preparation of *trans-p*-Methyl-α-phenylcinnamic Acid (20).

A modification of the method of Buckles and Brewer was employed in this reaction (21). *p*-Tolualdehyde (131 g., 1.10 moles), phenylacetic acid (158 g., 1.14 moles), triethylamine (115 ml., 0.82 mole) and acetic anhydride (250 ml., 1.25 moles) were refluxed together for 15 hours. The mixture was then steam distilled until the distillate was no longer cloudy. The residual crude acid mixture was brought to pH 10 with 6 N sodium hydroxide and the resulting solution was then continuously extracted with ether for 14 hours. The separation aqueous phase was heated until the solid dissolved, and the hot solution filtered on a sintered glass funnel containing a bed of activated charcoal on top of a bed of alumina. The filtrate was cooled and the sodium salt collected by filtration. The sodium salt was dissolved in hot water, and the solution acidified with dilute hydrochloric acid. The mixture was cooled and the free acid removed by filtration. The acid was dried in a vacuum oven at 70° to obtain 175 g. (70%) of the acid, m.p. 177.5-178.5°.

Anal. Calcd. for $C_{16}H_{14}O_2$: C, 80.64; H, 5.92; O, 13.43. Found: C, 80.58; H, 5.85; O (by difference), 13.57.

Preparation of Azine (**1**).

The above acid (15.0 g., 0.063 mole) was placed in a 200 ml. flask containing 50 ml. of thionyl chloride, and the mixture refluxed for 30 minutes. The excess thionyl chloride was removed under reduced pressure at 80°. The residue was dissolved in 25 ml. of tetrahydrofuran and the solution cooled to -75°. The solution was treated dropwise with cooling and stirring for more than one hour with a solution of lithium aluminum tritertiary butoxide (21) (16.0 g., 0.063 mole) in 50 ml. of tetrahydrofuran. The mixture was warmed to room temperature, poured onto crushed ice and filtered. The precipitate was washed with four 50 ml. portions of ethanol, the washings combined and treated with 85% hydrazine hydrate (1.0 g., 0.017 mole). The solution was refluxed for two hours, cooled and filtered to obtain 7.0 g. (50%) of yellow flakes, m.p. 190-191°.

Anal. Calcd. for $C_{32}H_{28}N_2$: C, 87.23; H, 6.41; N, 6.36. Found: C, 87.33; H, 6.49; N, 6.17.

Preparation of Compound 3.

The azine (1) (7.0 g., 5.9 mmoles) was placed in a flask and heated at 200° for 20 minutes. The resulting oil solidified on cooling and was recrystallized from methanol to obtain 6.0 g. (85%) of a white solid, m.p. 166-166.5°.

Anal. Calcd. for $C_{32}H_{28}N_2$: C, 87.23; H, 6.41; N, 6.36. Found: C, 87.25; H, 6.23; N, 6.21.

The nmr spectrum at 60 MHz in deuteriochloroform showed a singlet at 7.78 τ, singlet at 7.65 τ, singlet at 5.67 τ, singlet at 3.15 τ, multiplet at 2.93 τ and a singlet at 2.15 τ in a weight ratio of 3:3:2:1:18:1.

Pyrolysis of a Mixture of Azines 1 and 3.

Compound 3 (0.1 g., 0.38 mmole) and compound 1 (0.17 g., 0.38 mmole) were mixed and heated at 200° for 20 minutes. Thin layer chromatograms, infrared spectrum (chloroform) and ultraviolet spectrum of the product mixture were identical to those of an equimolar mixture of the pyrazoles 2 and 4.

β-Deuterocinnamic Acid.

Benzaldehyde-d (23) (20 g., 0.2 mole) was dissolved in pyridine (75 ml.) and malonic acid (20 g., 0.2 mole) and five drops of piperidine were added. The solution was left to stand for seven days at 40° and poured into ice and 20% sulfuric acid. The precipitated acid was filtered and air dried. Yield, 22 g. (77%), m.p. 131-133°.

β-Deuterocinnamaldehyde Azine (7).

This azine was prepared from the above acid by the procedure previously described, yield 60%, m.p. 179-180°.

Procedure for Kinetic Study of Pyrolysis of Cinnamaldehyde Azines.

Samples of the azine weighing between 10 mg. and 100 mg. contained in glass tubes were placed in a thermostated oil bath maintained at the specified temperature ± 1°. The samples were removed in turn at appropriate time intervals, ranging between 50 and 900 seconds, immediately plunged into ice water to freeze out unreacted azine, thereby quenching the reaction. Each sample was dissolved in ethanol and diluted to a concentration which was suitable for recording the ultraviolet spectrum. In all cases it was possible to directly determine the concentration of unreacted azine from the known extinction and the absorbance values near 3600 Å, a spectral region where the pyrazoles are transparent. The absorbance due to azine at the absorption maximum of the pyrazole (usually around 2500Å) was then calculated and subtracted from the total absorbance at that maximum to give the absorbance

due to pyrazole alone. In this way, both the disappearance of azine and the appearance of pyrazole were monitored.

Preparation of Benzyl Alcohol-O-D.

Benzyl alcohol (50 g., 0.46 mole) was repeatedly equilibrated with 5 ml. portions of 95% deuterium oxide until infrared analysis showed the percentage of benzyl alcohol-O-D to remain constant. This required six equilibrations, and the resulting benzyl alcohol contained approximately 80% benzyl alcohol-O-D as determined by infrared spectrometry.

Pyrolysis of Compound 3 in Benzyl Alcohol-O-D.

Compound 3 (5.0 g., 0.02 mole) was placed in 80% benzyl alcohol-O-D (43 g., 0.4 mole) and the mixture refluxed for 30 minutes. The solvent was removed under reduced pressure at 100°, b.p. 55-56° (0.2 mm). The product was collected at b.p. 145° (0.02 mm) in 90% yield, and identified as compound 4 by comparison of infrared and nmr spectra.

The nmr analysis of this fraction over seven proton integrations is summarized below.

Number of Benzylic Protons Per Indicated Proton Type

1.95/H (average)
1.92/H (pyrazolyl)
2.00/H (vinyl)
Average Value: 1.96

Pyrolysis of Compound 3 in Triphenylmethane-D (24).

A mixture of compound 3 (0.5 g., 1.9 mmoles) and triphenylmethane-D (4.0 g., 14 mmoles) was heated at 180° under nitrogen for 15 minutes. The mixture was cooled and dissolved in 15 ml. of hot ethanol. The bulk of the triphenylmethane-D (3.0 g.) crystallized upon cooling the ethanolic solution and was removed by filtration. The solution was evaporated to dryness, and the residue eluted with ether on a 1 x 25 cm. silica gel column. Early fractions contained 0.47 g. (94%) of an oil identified as compound 4 by comparison of infrared and nmr spectra. The nmr analysis of the oil over six proton integrations is summarized below.

Ratio Benzylic Protons to Proton Indicated

2.10/H (vinyl)
2.00/H (pyrazolyl)
Average Value: 2.05

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