8. E. Kyburz, H. Els, St. Majnoni, C. von Planta, A. Furst, and Pl. A. Plattner, Helv. Chim. Acta, 49, 359 (1966).
9. É. É. Liepin'sh, I. Ya. Kalvin'sh, and P. T. Trapentsier, Khim. Geterotsikl. Soedin., No. 11, 1231 (1984).

MECHANISM OF THE FISCHER REACTION. REARRANGEMENT OF CYCLOHEXANONE N-METHYLPHENYLHYDRAZONE AND N,N'-DIMETHYL-N-PHENYL-N'-(1-CYCLOHEXENYL)HYDRAZINE TO 9-METHYL-1,2,3,4-TETRAHYDROCARBAZOLE

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The kinetics of the thermal and acid-catalyzed Fischer reaction of cyclohexanone N-methylphenylhydrazone and N,N'-dimethyl-N-phenyl-N'-(1-cyclohexenyl)hydrazine were studied by a spectrophotometric method. Formation of the carbon—carbon bond proceeds by a [3,3]-sigmatropic shift mechanism. This conclusion was confirmed by MINDO/3 calculations of the rearrangement of a model divinylhydrazine.

We have previously reported [1, 2] that the key step in Fischer indolization (the formation of a carbon—carbon bond) goes via a [3,3]-sigmatropic rearrangement. This conclusion was based on the small effect of substituents on the proportions of isomeric N-aryltetrahydrocarbazoles that form in this reaction from unsymmetrically substituted cyclohexanone N,N-diarylhydrazones. Moreover, in a study of intramolecular Stolle cyclization of metasubstituted chloroacetyldiarylamines we established that there is a high selectivity of carbocation attack on phenyl nuclei with more-donor-like substituents [3]. In combination with the data of [1, 2], these results, in our view, indicate the unsuitability of approaching the fundamental step of the Fischer reaction as an electrophilic substitution.

For a deeper understanding of the indolization mechanism it was necessary to obtain the kinetic and thermodynamic process parameters and also to perform quantum mechanical calculations.

There are several publications [4-7] in which the cyclization rate in acid medium has been measured for various type I hydrazones substituted in the benzene and cyclohexanone rings (see Scheme 1). The kinetic results of [4-6] have been thoroughly discussed in a review [8].

Scheme 1

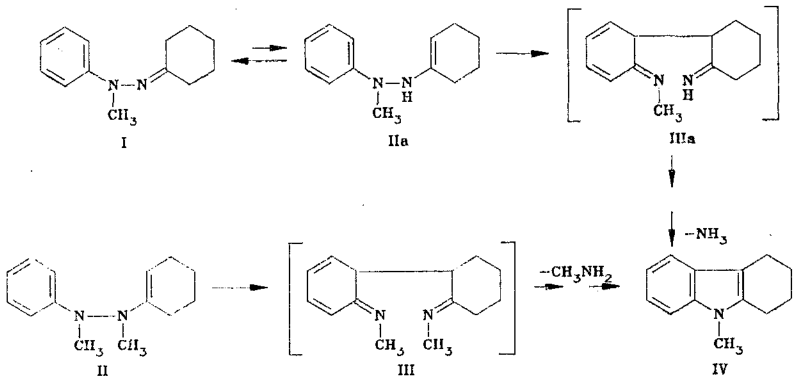

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TABLE 1. Rate Constants and Activation Parameters of I → IV Reaction

Reaction conditions		Thermal reaction			Acid-catalyzed reaction					
					H_2SO_4—I, 2 : 1			$(CH_3)_3CCOOH$—I, 2 : 1		
Solvent	T, °C	$k \cdot 10^5 sec^{-1}$	$\Delta H^{\neq}$ ±0,2 kcal/mole	$\Delta S^{\neq}$, eu	$k \cdot 10^5 sec^{-1}$	$\Delta H^{\neq}$ ±0,2 kcal/mole	$\Delta S^{\neq}$, eu	$k \cdot 10^5 sec^{-1}$	$\Delta H^{\neq}$ ±0,2 kcal/mole	$\Delta S^{\neq}$, eu
Ethylene glycol	60	0,31	15,5	−37±1	2,86	13,8	−42,6±0,8	0,35	16,2	−36±1
	80	1,24			10,00			1,41		
	120	13,05			80,96			14,40		
Diamyl ether	60	0,28	16,2	−36±1	2,65	14,5	−36,1±0,8	0,38	15,5	−37±1
	80	1,20			9,82			1,50		
	120	14,05			89,22			16,58		
Decane	60	0,21	17,4	−32±1						
	80	1,00								
	120	13,75								

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*At 0.1:1 and 20:1 H_2SO_4:I ratios, rate constants for I → IV in ethylene glycol are respectively $2.2 \cdot 10^{-5}$ (60°) and $24.7 \cdot 10^{-5}$ (50°), while in presence of CH_3ONa (2 moles per mole of I), $k = 1.30 \cdot 10^{-5}$ (80°).

TABLE 2. Rate Constants and Activation Parameters of II → IV Reaction

Solvent	Thermal reaction				Acid-catalyzed reaction						
					H_2SO_4—II, 2 : 1				$(CH_3)_3CCOOH$—II, 2 : 1		
	T, °C	$k \cdot 10^5 sec^{-1}$	$\Delta H^{\neq}$ ±0,2 kcal/mole	$\Delta S^{\neq}$, eu	T, °C	$k \cdot 10^5 sec^{-1}$	$\Delta H^{\neq}$ ±0,2 kcal/mole	$\Delta S^{\neq}$, eu	$k \cdot 10^5 sec^{-1}$	$\Delta H^{\neq}$ ±0,2 kcal/mole	$\Delta S^{\neq}$, eu
Ethylene glycol	60	1,49	15,0	−36±2	44	226,8	13,4	−31±1	18,2	14,3	−30±1
	70	2,92			50	342,8			27,2		
	80	5,70			60	660,0			56,1		
Diamyl ether	60	1,28	14,8	−37±2	44	211	12,9	−31±1	12,4	14,7	−29±1
	70	2,48			50	310			18,8		
	80	4,90			60	590			39,7		
Decane	60	2,11	15,0	−36±2							
	70	1,08									
	80	4,10									

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*At 0.1:1 and 20:1 H_2SO_4:II ratios, rate constants for II → IV in ethylene glycol are respectively $228 \cdot 10^{-5}$ (50°) and $445 \cdot 10^{-5}$ (30°), while in the presence of CH_3ONa) (2 moles per mole of II), $k = 5.8 \cdot 10^{-5}$ (80°).

One of the fundamental conclusions of the authors of [4-8] was that the rate-determining step of the Fischer reaction was the acid-catalyzed tautomeric conversion of hydrazone I to enehydrazine IIa. We note that except for semiquantitative measurements [9, 10], there are no kinetic data on the rearrangement of type II enehydrazines. Moreover, in [4-7] only the kinetics of the acid-catalyzed reaction was studied, but not yet the kinetics of the thermal process.

In the present work we report a spectrophotometric study of the kinetics of the rearrangements of cyclohexanone N-methylphenylhydrazone (I) and N,N'-dimethyl-N-phenyl-N'-(1-cyclohexenyl)hydrazine (II) to 9-methyl-1,2,3,4-tetrahydrocarbazole (IV).

In choosing hydrazone I and enehydrazine II as model compounds, we started from the fact that these compounds form IV easily and in high yield, and the rearrangement of II permits the study of the principal fundamental step of the Fischer reaction in "pure form," viz., the change of hydrazine II to dienonimine III. Finally, in the comparison of the rates of the two processes I → IV and II → IV, we can estimate the contribution of the isomerization step I $\rightleftarrows$ IIa to the overall process rate (if we do not take account of the possible effect of the CH_3 at the β-nitrogen atom.)

In investigating the rearrangement kinetics of I and II, we studied the effects of solvent (ethylene glycol, diamyl ether, decane) and acidity (sulfuric acid in various proportions, trimethylacetic acid) on the rate of formation of the tetrahydrocarbazole IV.

The kinetic results and the energy parameters of the reactions I → IV and II → IV are shown in Tables 1 and 2.

In considering the kinetic data it is necessary to distinguish the following fundamental features.

First of all, both the thermal and the acid-catalyzed rearrangements of II are faster than the respective reactions of I. It follows that the isomerization step I $\rightleftarrows$ IIa makes a substantial contribution to the overall rate of IV formation. Second, the nature of the solvent has little effect on the reaction rate. Third, in all the cases studied the Fischer reaction is first order and has quite high negative activation entropy. From the latter two conclusions we can assign this rearrangement to the class of concerted [3,3]-sigmatropic processes.

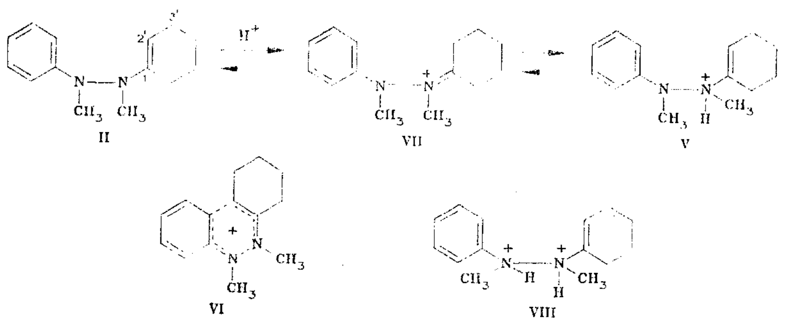
Let us now consider the effect of acidity on reaction rate in more detail. Table 2 shows that the acceleration factor of enehydrazine rearrangement catalyzed by sulfuric acid (2 moles H_2SO_4 per mole of reagent) is ∿400 at 60° relative to the thermal rearrangement. Since the rate-determining step of II rearrangement is formation of the carbon—carbon bond (as confirmed by the complete identity of the rate constants calculated with respect to reagent and product), the strong acceleration in the presence of acid is evidence for a charge-induced peri-cyclic reaction [11]. This conclusion agrees with the data of [9, 10]. The reaction is so fast because in the six-membered state VI the positive charge is not localized at a nitrogen atom, as shown, e.g., in V, but is delocalized to a definite extent over all six atoms (Scheme 2). An analogous acceleration occurs in the acid-catalyzed aromatic amine Claisen rearrangement, for which charge delocalization in the transition state was confirmed by the Hückel Molecular orbital method and the theory of first order perturbation [12].

The rearrangement of I is accelerated about tenfold in the presence of 2 moles of sulfuric acid. Our rate constant values are close to those given in [7] for the sulfuric acid-catalyzed reaction in aqueous methanol. The concentration and strength of the acid have a noticeable effect on the indolization rates of I and II. Thus, addition of sulfuric acid at 0.1 mole per mole of reagent causes a smaller acceleration than at a 2:1 ratio, while a larger excess of acid causes additional increase of the rate constant (see Tables 1, 2).

These data can apparently be explained as follows. As shown in [9, 10], protonation of type II ene hydrazines occurs at $C_{(2)}$ of the cyclohexane ring to form the hydrazonium salt VII, which in solution is in equilibrium with the ene hydrazine salt V (Scheme 2). Moreover it is known that the energy of the bonding molecular orbits of 1- and 2-azaallylic systems with a positive charge is less than the energy of the MO of the corresponding uncharged system [13].

This particular combination of two azaallylic radicals is the transition state of the aza-cope rearrangement (the Fischer reaction is a special case of this reaction), which also accelerates in the presence of acid [13]. It follows that a type V compound is more reactive

Scheme 2



than ene hydrazine II. The higher the acid concentration, the higher will be the concentrations of the protonated forms VII and V, and therefore the higher will be the reaction rate, since the basicity of ene hydrazines is low.

Such a feature is observed experimentally. Moreover it is impossible to exclude the possible formation of the diprotonated molecules VIII (in the presence of a greater excess of acid), in which cleavage of the nitrogen—nitrogen bond becomes yet easier. On the other hand such a weak acid as trimethylacetic can not protonate II as efficiently as sulfuric acid. Therefore the rate of the reaction catalyzed by trimethylacetic acid is noticeably less than that in the presence of sulfuric acid.

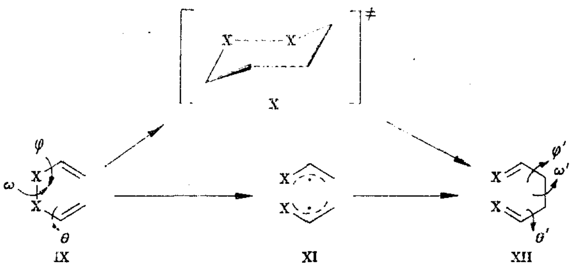
Addition of sodium methylate (2 moles per mole of reagent) to the reaction mixture does not appreciably affect the indolization rates of I and II. This result points to the absence of alkaline catalysis in the Fischer reaction. A similar qualitative conclusion was drawn in [14].

Thus our data on the effect of acidity on the rate of the Fischer reaction do not conflict with the concept of the concerted nature of the formation of the carbon—carbon bond (II → III).

We presumed that a quantum chemical study of this reaction could give additional information concerning its mechanism.

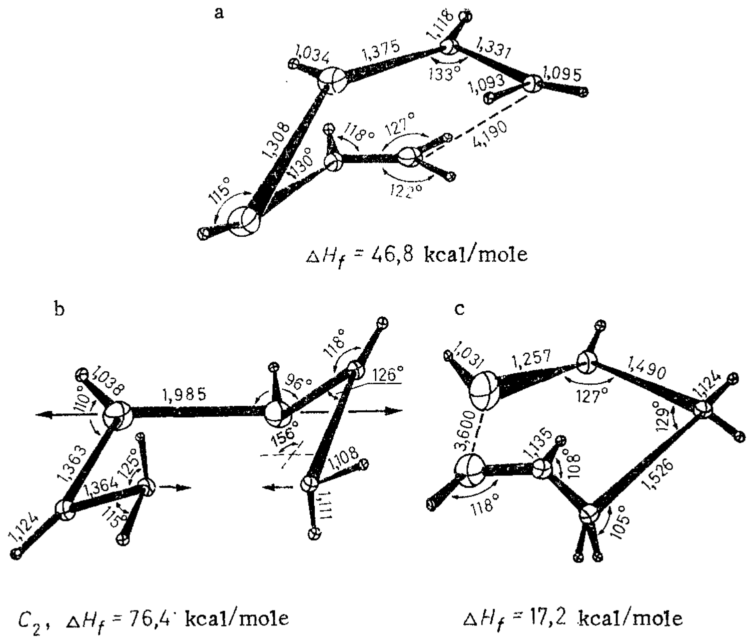
Step II → III, described by the model mechanism of a [3,3]-sigmatropic migration (in Scheme 3, X = NH), has been studied in detail for a whole series of experiments [15] for the hydrocarbon analog ($X = CH_2$): (see Scheme 3).

Scheme 3



But until recently even the mechanism of the [3,3]-sigmatropic reaction in 1,5-hexadiene ($X = CH_2$) remained in question; it was not clear to start with, whether it was concerted (IX → X → XII) or stepwise (IX → XI → XII). Early experimental work [16, 17] on the stereochemistry of the reaction did not permit a choice between the two mechanisms. Thermodynamic calculations [18] by an additive scheme [19] indicated the concerted nature of the Cope rearrangement. But although MINDO/3 calculations [20] showed the presence in the minimum energy reaction path of a local minimum corresponding to the structure of X ($X = CH_2$), the depth of the minimum was no more than 3 kcal/mole. This did not permit the Cope rearrangement to be unequivocally classified as non-concerted, because it is known that the MINDO/3 method overestimates the stability of hypervalent structures [21]. Inclusion of a configuration interaction in the MINDO/3 calculations [20] sharply stabilized the structure of the intermediate, and pointed to the stepwise nature of the mechanism.

Very recent studies [18] of secondary kinetic isotope effects in the rearrangements of substituted 1,5-hexadienes have unequivocally shown the concerted nature of the Cope reac-



ΔH_f = 46,8 kcal/mole

C_2, ΔH_f = 76,4 kcal/mole

ΔH_f = 17,2 kcal/mole

Fig. 1. Geometry of the IX → XII rearrangement, calculated by MINDO/3. a) initial b) transitional c) final. Numbers along bonds are bond lengths, Å.

tion. Thus the inclusion of CR in a semiempirical MINDO/3 scheme gives erroneous results because of the error in configurational parametrization [22]. MINDO/3 calculations without allowance for CR agree quite well with experimental data in representing both the activation barriers and the energy differences between chair and boat conformations of the transitional states. Keeping this circumstance in mind, in the present work we have used MINDO/3 in a one-determinant approximation to study the rearrangement of the model substance divinylhydrazine IX (X = NH).

In the group state, IX, and the final state, XII, of the reaction the molecules tolerate hindered internal rotation about the angles ω, φ , and θ. We did not study the total potential energy surface (PES) of isomerization along the three angles, but estimated only the relative stability of the individual conformations.

The most stable form of IX is the gauche conformation with $\omega = 62^\circ$ ($\Phi = \theta \sim 0^\circ$) (Fig. 1). According to calculations the most stable form of XII is the full trans structure with $\varphi = \theta = \omega \sim 180^\circ$, which differs from the gauche conformation ($\Phi = 53^\circ$, $\theta = \varphi = 0^\circ$) by 5 kcal/mole. Since the rearrangement of divinylhydrazine necessarily goes through the gauche conformation of XII, we will also consider it to be the final step in the elementary reaction of Scheme 3.

The minimum energy path of the IX–XII reaction was determined by probing the potential energy surface by the reaction coordinate method [23, 24], directed at a localization of the structures of the transition states. A transition state structure was identified by calculating a force-constant matrix and checking its fitness by the requirements of a Murrell–Laidler theorem [25]. The minimum-energy reaction path (internal reaction coordinate [26, 27]) was determined as the path of the most rapid drop from the transition-state point along the two directions indicated by the transition vector [28] into the potential-energy-surface minimum lying along two sides of the transition state. The minimum-energy reaction path thus constructed for IX → XII is shown in Fig. 2, and the geometry of the transition state is shown in Fig. 1,b.

The MINDO/3 calculations showed that the transition state X of the [3,3]-sigmatropic migration has the chair structure (C_2 symmetry). Such geometry for X can be considered from the viewpoint of perturbation theory as the result of the interaction of two $H\dot{N}CH{=}CH_2$ radicals [29]; here the effect of the interaction is first of all to change the π-MO of the radicals. We carried out special MINDO/3 calculations in a one-determinant approximation of the electron structure of the azaallyl radical $H\dot{N}CH{=}CH_2$; they showed that the ground state is a σ-type. But for the isoelectronic $\dot{O}CHO$ radical, very accurate *ab initio* multiconfiguration self-consistent field calculations showed that although the ground state of the radical is

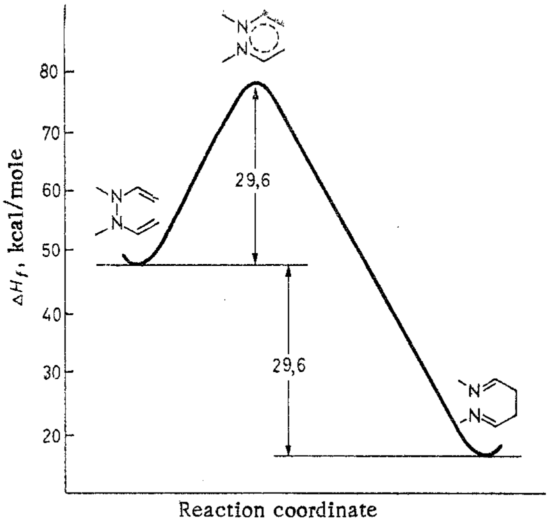


Fig. 2. Minimum-energy path for IX-XII reaction, calculated by MINDO/3.

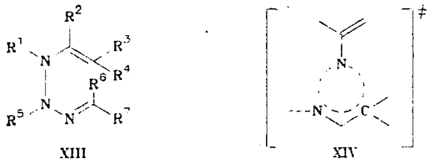
σ-type ($^2B_2$), nevertheless the excited π-type state ($^2A_2$) is located very close to its; the energy difference of the states is ∿6.2 kcal/mole).* For other isoelectronic radicals the σ- and π-electron states are also quite close together in energy [31, 32]. It can thus be presumed that in the case of the azallyl radical the σ- and π-states are close together, so that π-MO take part effectively when two such systems interact.

The established geometry of the transition state X is evidence of a similarity in the orbital consideration of [3,3]-migration in 1,5-hexadiene and in intermediate IX. Such an analysis has already been carried out for 1,5-hexadiene in [33]; the two possible mechanisms-via the chair and boat transition states—are equally permissible, and consideration of the secondary orbital interactions gives preference to the first migration mechanism. When the results of our calculations are taken into account it can also be concluded that the IX → XII rearrangement through the transition state X is permissible.

Analysis of the changes in the one- and two-center components of the total energy shows that to a very large extent they are related to the carbon and nitrogen atoms in state X. Charge transfer takes place between these atoms and the periphery of the cyclic system of X (i.e., the hydrogens). The total electron population density at the six centers decreases by 0.133 $\bar{e}$ in the transition from IX to X.

It follows that substituents that increase the electronegativity of the atoms of the six-center ring in X ought to stabilize the transition states and accelerate the [3,3]-shift. At the same time the transition to the aza analog XIII ought to be accompanied by an increase in energy barrier.

Scheme 4



XIII XIV

It should also be noted that the concerted mechanism IX → X → XII is not the only one possible for a [3,3]-shift; a [1,3]-shift via the strained four-center transition state XIV is an alternative. But according to the MINDO/3 calculations, a concerted [1,3]-shift can not compete with a [3,3]-shift, because transition state XIV is 49.2 kcal/mole higher in energy than X.

The stepwise mechanism that includes the formation of the radical pair XI is also energetically less favored (by 8.2 kcal/mole) than the concerted mechanism of the [3,3]-

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*One-determinant MINDO/3 calculations showed that the formyl radical ground state is also σ-type.

shift. But such a trivial energy difference between the two migration mechanisms is evidence for the substantial contribution of homolysis to the overall rearrangement scheme of the IX system.*

Thus, as was to be expected, the II → III rearrangement predominantly follows the path of the concerted [3,3]-sigmatropic shift.

EXPERIMENTAL

Cyclohexanone N-methylphenylhydrazone (I) was obtained according to [6] from N-methylphenylhydrazine and cyclohexanone. UV spectrum (ethylene glycol), λ_{max} (log ε): 252 (3.94), 290 nm (3.43).

N,N'-Dimethyl-N-phenyl-N'-(1-cyclohexenyl)hydrazine (II) was obtained according to [9] from N,N'-dimethylphenylhydrazine and cyclohexanone; bp 89-93° (0.01 mm). According to [9], bp 90-95° (0.01 mm). UV spectrum ethylene glycol), λ_{max} (log ε): 250 (3.85), 294 nm (3.56).

9-Methyl-1,2,3,4-tetrahydrocarbazole (IV) was obtained from N-methylphenylhydrazine and cyclohexanone according to [9], mp 50-51° (from dilute alcohol); according to [9], mp 50-51°. UV spectrum (ethylene glycol), λ_{max} (log ε): 234 (4.60), 288 nm (3.87).

Procedure for Kinetic Measurements. Standard solutions of hydrazone I and ene hydrazine II were prepared in the appropriate solvent so that reagent concentration would be 10^{-4}-10^{-5} M. An aliquot of solution was placed in a 5 ml ampul. The ampul was sealed and heated in a thermostat in which the temperature was maintained within ±0.1°. At definite time intervals the ampuls were removed from the thermostats, cooled quickly in ice water, and opened. The contents were transferred to a cuvet and the UV spectrum was obtained on a Hitachi EPS-3T instrument. When the reaction was carried out in acid, the required amount of acid was prepared separately and mixed with the standard solution of reagent immediately before the start of the reaction. To carry out the reaction below 80°, a thermostated spectrophotometer cuvet was used.

Rate constants were obtained by the first-order equation:

$$K=\frac{2,303}{t}\log\frac{D_0-D_\infty}{D-D_\infty},$$

Here D is the optical density of hydrazone I, ene hydrazine II, or tetracarbazole IV at the respective λ_{max} at a particular time; D_0 is the optical density at the start of the reaction; D_∞ is the optical density at the end of the reaction. For D_∞ we took the optical density of a tetracarbazole solution at 100% conversion. The rate constants given in Tables 1 and 2 are the averages of three measurements. When the reaction is carried out under identical conditions with sample removal at one time, the error in K does not exceed 3%.

Calculation Procedure. MINDO/3 calculations were carried out [34] by a program [35] adapted for a BESM-6 computer by I. I. Zakharov. The stationary points on the potential energy surface were identified by calculation of a force-constant matrix according to [36].

LITERATURE CITED

1. N. M. Przheval'skii, I. I. Grandberg, and N. A. Klyuev, Khim. Geterotsikl, Soedin., No. 8, 1065 (1976).
2. N. M. Przheval'skii, I. I. Grandberg, N. A. Klyuev, and A. B. Belikov, Khim. Geterotsikl. Soedin., No. 10, 1349 (1978).
3. N. M. Przheval'skii, and I. I. Grandberg, Khim. Geterotsikl. Soedin., No. 7, 940 (1982).
4. K. H. Pausacker and C. I. Schubert, J. Chem. Soc., No. 7, 1814 (1950).
5. I. McLean, S. McLean, and R. I. Reed, J. Chem. Soc., Part 3, 2519 (1955).
6. P. I. Th. Scheltus, Kinetic Investigations of the Fischer Indole Synthesis, Dissertation, Leiden (1959).
7. R. N. Elgersma, Some Aspects of the Fischer Indole Synthesis, Dissertation, Rotterdam (1969).

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*According to MINDO/3 calculations [20] for the Cope rearrangement in 1,5-hexadiene, the concerted mechanism via the "chair" transition state is 33.4 kcal/mole more favored than the stepwise mechanism that involves formation of the radical pair XI (X = CH_2).

8. I. I. Grandberg and V. I. Sorokin, Usp. Khim., 43, 266 (1974).
9. P. Schiess and A. Greeder. Helv. Chim. Acta, 57, 2643 (1974).
10. P. Schiess and E. Sendi, Helv. Chim. Acta, 61, 1364 (1978).
11. U. Widmer, J. Zcindely, H.-J. Hansen, and H. Schmid, Helv. Chim. Acta, 56, 75 (1973).
12. S. Jolidon and H.-J. Hansen, Helv. Chim. Acta, 60, 978 (1977).
13. H. Heimgartner, H.-J. Hansen, and H. Schmid, in: Iminium Salts in Organic Chemistry, Wiley, New York (1979), p. 655.
14. D. N. Plutitskii, Candidate's Dissertation, Chem. Sci., Moscow (1983).
15. S. J. Rhoads and N. R. Raulins, Org. React., 22, 1 (1975).
16. W. E. Doering and W. R. Roth, Tetrahedron, 18, 67 (1962).
17. R. K. Hill and N. W. Gilman, Chem. Commun., 619 (1967).
18. J. J. Gajewski, Acc. Chem. Res., 13, 142 (1980).
19. S. W. Benson, Thermochemical Kinetics, 2nd edn., Wiley, New York (1976).
20. M. J. S. Dewar, G. P. Ford, M. L. McKee, H. Rzepa, and L. E. Wade, J. Am. Chem. Soc., 99, 5069 (1977).
21. M. Flanigan, E. Komornieki, and J. MacIver, in: Semiempirical Methods of Calculating Electron Structure, G. Segal, ed. Plenum Press (1977).
22. K. Freed, in: Semiempirical Methods of Electron Calculating G. Segal, ed., Plenum Press (1977), Vol. 1, Mir, Moscow (1980), p. 271.
23. M. J. S. Dewar, Chem. Brt., 11, 95 (1975).
24. K. Muller, Angew. Chem. Int. Ed, 19, 1 (1980).
25. J. N. Murrell and K. J. Laidler, Trans. Faraday Soc., 64, 371 (1968).
26. K. Fukui, J. Phys. Chem., 74, 4161 (1970).
27. M. V. Basilevsky, Chem. Phys., 24, 81 (1977).
28. R. W. Stanton and J. V. McIver, J. Am. Chem. Soc., 97, 3632 (1975).
29. M. J. S. Dewar and L. E. Wade, J. Am. Chem. Soc., 99, 4417 (1977).
30. D. Feller, E. S. Huyser, W. T. Borden, and E. R. Davidson, J. Am. Chem. Soc., 105, 1459 (1983).
31. N. C. Baird and K. F. Taylor, Can. J. Chem., 58, 733 (1980).
32. M. J. S. Dewar, A. H. Parker, and A. B. Pierini, J. Am. Chem. Soc., 104, 3242 (1982).
33. R. Woodward and R. Hoffmann, Conservation of Orbital Symmetry Academic Press (1970).
34. R. C. Bingham, M. J. S. Dewar, and D. H. Lo, J. Am. Chem. Soc., 97, 1285 (1975).
35. QCPE, Program N 279, Indiana Univ., Bloomington, Indiana, 47401, U.S.A.
36. M. J. S. Dewar and A. Komornicki, J. Am. Chem. Soc., 99, 6147 (1977).