

Amino Ketone Rearrangements. V. A Kinetic Analysis¹

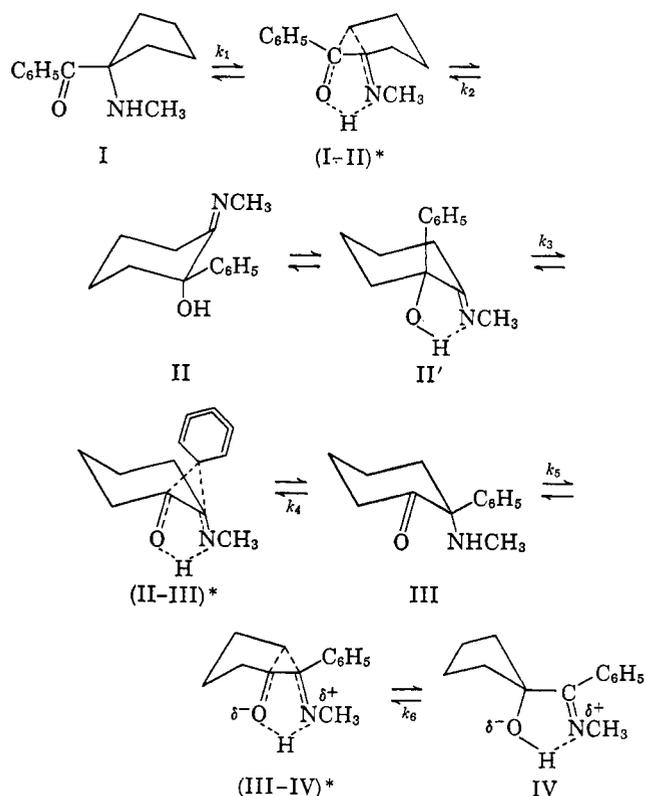
Calvin L. Stevens, Harry T. Hanson, and K. Grant Taylor

Contribution from the Department of Chemistry, Wayne State University, Detroit, Michigan 48202. Received December 8, 1965

Abstract: A kinetic analysis at three temperatures of the I-IV rearrangement has been done. The rate constants of five of the six reactions involved have been obtained with the aid of a computer. Activation parameters for the five reactions have been calculated, and the mechanisms of the rearrangements are discussed.

The thermal rearrangement of α -amino ketones bearing dialkyl substituents at the α carbon atom has been seen to develop as a general reaction.^{1,2a-d} The general thermal rearrangement of structurally related α -hydroxyimines has proved to be of synthetic^{2c-g} and theoretical^{1,2g} interest. The general rearrangement has been visualized as encompassing a four-component equilibrium,^{1,2g} as exemplified by compounds I, II, III, and IV (in Scheme I) for the specific

Scheme I



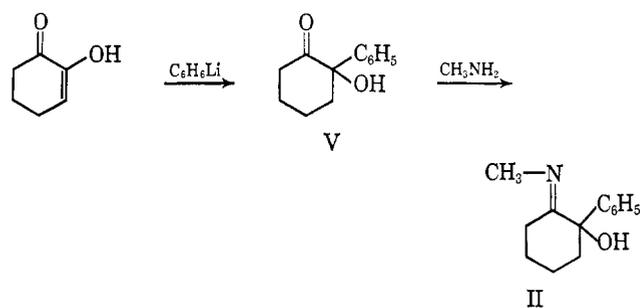
case of the cyclopentyl phenyl ketone-2-phenylcyclohexanone carbon skeleton system. A previous kinetic

(1) (a) Abstracted in part from the Ph.D. dissertation of H. T. Hanson, Wayne State University, 1965; (b) paper IV: C. L. Stevens, I. L. Klundt, M. E. Munk, and M. D. Pillai, *J. Org. Chem.*, **30**, 2967 (1965).

(2) (a) C. L. Stevens, R. D. Elliott, and B. L. Winch, *J. Am. Chem. Soc.*, **85**, 1464 (1963); (b) C. L. Stevens, R. D. Elliott, B. L. Winch, and I. L. Klundt, *ibid.*, **84**, 2272 (1962); (c) C. L. Stevens, A. B. Ash, A. Thuillier, J. H. Amin, A. Balys, W. E. Dennis, J. P. Dickerson, R. P. Gliniski, H. T. Hanson, M. D. Pillai, and J. W. Stoddard, *J. Org. Chem.*, in press; (d) C. L. Stevens, A. Thuillier, K. G. Taylor, F. A. Daniher, J. P. Dickerson, H. T. Hanson, N. A. Nielsen, N. A. Tikotkar, and R. M. Weier, *ibid.*, in press; (e) D. F. Morrow, M. E. Brokke, G. W. Moersch, M. E. Butler, C. F. Klein, W. A. Nenklis, and E. C. Y. Huang, *ibid.*, **30**, 212 (1965); (f) D. F. Morrow, M. E. Butler, and E. C. Y. Huang, *ibid.*, **30**, 579 (1965); (g) C. L. Stevens, A. Thuillier, and F. A. Daniher, *ibid.*, **30**, 2962 (1965).

study,^{2b} a Hammett $\sigma\rho$ analysis, took advantage of the high yield, irreversible nature which characterized the thermal rearrangement of the N-phenyl analog of IV to the N-phenyl analog of III. Those same characteristics prevailed for the rearrangement of IV itself to III, thus permitting a detailed kinetic analysis by similar experimental techniques. It was soon apparent, however, that in the thermolysis of I a much more complex kinetic situation prevailed, and, indeed, the intervention of II (in substantial concentration) as an intermediate in the conversion of I to III^{2a} was demonstrated for the first time. Accordingly, a kinetic analysis of the entire I-IV rearrangement was undertaken with the hope of more clearly delineating the mechanistic requirements for rearrangement at each stage. This paper reports these results.

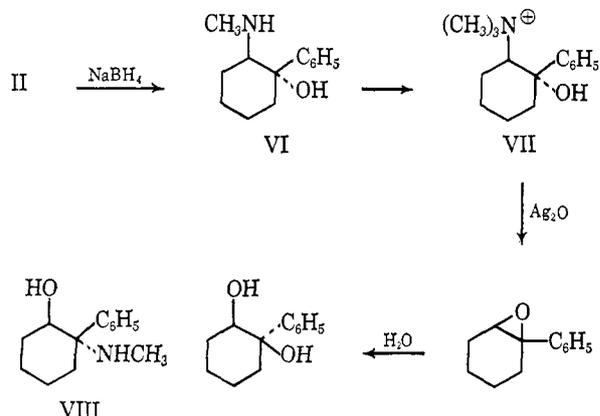
Syntheses and Preliminary Studies. The isomeric α -amino ketones I and III have been reported previously.^{2a} Hydroxyimine IV was prepared from 1-benzoyl-1-bromocyclopentane by an established procedure,³ and its rearrangement was the chief synthetic source of amino ketone III. The synthesis of hydroxyimine II was undertaken through 2-hydroxy-2-phenylcyclohexanone (V), which, in turn, was prepared by the method of Tombouliau.⁴ Treating V in liquid methylamine at room temperature for 5 days were optimum conditions for the preparation of II, a liquid. More vigorous conditions gave much lower yields and



II was seen to be somewhat unstable to the atmosphere and light. The infrared spectrum (ν 3280 and 1680 cm^{-1}) supported the assigned structure, but the instability of II warranted a proof of structure. Thus, borohydride reduction of II afforded a crystalline amino alcohol VI isomeric with VIII, the reduction

(3) (a) C. L. Stevens, P. Blumbergs, and M. E. Munk, *ibid.*, **28**, 331 (1963); (b) performed by Dr. A. Thuillier.

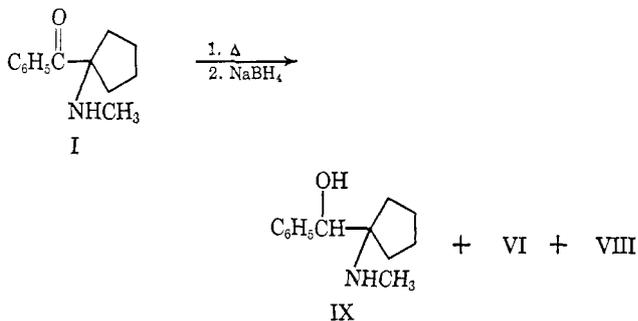
(4) P. Tombouliau, *J. Org. Chem.*, **26**, 2652 (1961), reports V as a liquid while I. Elphimoff-Felkin, G. LeMyet, and B. Tchouber, *Bull. Soc. Chim. France*, **522**, 581 (1958), report V, prepared by a different route, as a solid, mp 68–69.5°. After extensive purification followed by long standing, our liquid V crystallized, mp 68–70°, thus resolving an apparent literature conflict.



product of amino ketone III.⁵ Clarke-Eschweiler methylation and methyl iodide treatment afforded methiodide VII, which, on mild treatment with ethanolic silver oxide, afforded 1-phenylcyclohexene oxide.⁶ Hydrolysis of the oxide gave the known *cis*-2-hydroxy-2-phenylcyclohexanol.⁷ Thus, this series of reactions demonstrated the structure and stereochemistry of hydroxyimine II.

The initial rearrangement studies of I were devoted to the isolation of reaction products and intermediates and determining the material balance of the reaction. In the process, standard rearrangement conditions were devised which were used for both the qualitative and quantitative experiments (details in the Experimental Section). In general, high-boiling hydrocarbons were used as solvents and were maintained near their monitored, reflux temperatures by a Woods metal bath. Slow helium flow provided an inert atmosphere.

Under these conditions the presence of II in the rearrangement was demonstrated by brief heating of I (12 min, *n*-tridecane, 235°) and then quenching the reaction. The entire reaction mixture was subjected to borohydride reduction and the resulting mixture of alcohols examined by thin layer chromatography. Analytical tlc revealed the presence of alcohols VI, VIII, and IX. Preparative tlc was successfully employed for separation and alcohols IX (38%) and VI (16%) were isolated as their hydrochloride salts. The low percentage of VIII precluded its isolation.



Next, the rearrangement behavior of the intermediate II was examined. Thermolysis of II (3 hr, *n*-tridecane, 235°) followed by aqueous acid hydrolysis

(5) Amino alcohol VIII has been previously reported as a mixture of diastereomers.^{2a} Alumina chromatography afforded the *trans* isomer VIII in 80% yield. The *trans* configuration was established by a method similar to that used for VI and is reported on in ref 2c.

(6) Identified by infrared comparison with an authentic sample: S. Nametkin and N. Iwanoff, *Ber.*, **56B**, 1805 (1923).

(7) J. Boeseken, *ibid.*, **56B**, 2409 (1923).

afforded a basic fraction from which amino ketone I (24%) and amino ketone III (51%) could be isolated after chromatography.

While amino ketones of type III have appeared to be the most thermally stable type,^{1,2} and while the rearrangement of IV to III exhibited no systematic downward drift of rate constants, the reversible nature of the formation of III from hydroxyimine II was demonstrated in the following experiment. Thermolysis of III (3 hr, *n*-tridecane, 235°) produced a reaction mixture whose infrared spectrum revealed, in addition to the carbonyl absorption of III (1740 cm^{-1}), a sharp absorption at 1680 cm^{-1} (C=O, C=N) indicative of the presence of I and/or II. Analytical thin layer chromatography of the reaction showed three spots with R_f values corresponding to compounds I, II, and III. No IV was detectable by infrared (1650 cm^{-1} , C=N).

To establish the validity of the analytical technique and the calculations employed for the kinetic studies, it was necessary to demonstrate that mass was conserved in the form of the three isomers, I, II, and III. Hence, I was heated well past its rearrangement half-life under standard conditions (2.5 hr, *n*-tridecane, 235°). Then the reaction was quenched and treated with excess sodium borohydride as before. The basic materials were isolated and spotted in thin layer chromatography where only the three spots for VI, VIII, and IX could again be seen. All the basics were then converted to a colorless mixture of crystalline hydrochlorides which was found to represent 95% of the weighed amount of starting material. The reaction temperature of 235° was chosen for this experiment since it represented the most rigorous rearrangement conditions studied.

The Kinetic Study. For the rearrangement of hydroxyimine IV to III, progress of the reaction was followed by infrared (see the Experimental Section). Comparison of the carbonyl band intensity at 1740 cm^{-1} with that of a prepared calibration curve revealed the concentration of III. The rate constants, k_6 , were determined by applying the weighted least-squares method of Roseveare,⁸ and these are listed in Table I. The experiments using *o*-dichlorobenzene solvent (runs 5 and 6) showed the reproducibility of the technique as well as demonstrating a solvent effect (compare runs 6 and 7). The rearrangement in decalin solvent at 167° (run 3) was performed to exclude the possibility of a solvent effect between cyclic and acyclic hydrocarbons. Because of a larger than usual experimental temperature variation during run 3 it was excluded, along with runs 5 and 6, from use in calculating E_a .

Within the limits of experimental technique, the rearrangement of IV to III was irreversible. However, in the experiment testing the thermal stability of III (*vide supra*), it was estimated that 1% of IV could escape infrared detection. Using this as a maximum value for the amount of hydroxyimine IV present, it was possible to estimate a $\text{IV} \rightleftharpoons \text{III}$ equilibrium constant of $\sim 10^2$ and a ΔF^{235} of -4.6 kcal.

The reaction of I was followed accurately by monitoring the disappearance of the 242- $\text{m}\mu$ ultraviolet maximum of I in reaction aliquots. Infrared could again be used to follow the appearance of III, but this time with reduced accuracy due to the proximity of absorption resulting from the superimposed C=O

(8) W. E. Roseveare, *J. Am. Chem. Soc.*, **53**, 1654 (1931).

Table I. Rate Constants for the Amino Ketone Rearrangements^a

Run	Temp, °C	Solvent	k_1	k_2	k_3	k_4	k_5	Dev ^b
1	155	<i>n</i> -Nonane					0.039	
2	166	<i>n</i> -Decane					0.27	
3	167	Decalin					0.22	
4	174	<i>n</i> -Decane	0.25	0.87	0.16	0.1		1.3
5	181	[<i>o</i> -Dichloro- benzene]					1.4	
6	181						1.7	
7	184	Decalin					0.80	
8	190	Decalin	0.72	1.3	0.20	0.1		1.3
9	235	<i>n</i> -Tridecane	8.4	16	1.6	0.6		0.74
10 ^c	235	<i>n</i> -Tridecane	8.5	11	1.6	0.6		2.6

^a Subscript numerals refer to k 's indicated in Scheme I; units are $\text{min}^{-1} \times 10^2$. ^b Difference between experimental and computer calculated concentrations of I at time t , averaged, expressed as mg/ml; Figure 1 and data in Table III illustrated the concentration ranges used. ^c Reaction using pure II as starting material.

and C=N bands of I and II at 1680 cm^{-1} . Previous qualitative data indicated an $A \rightleftharpoons B \rightleftharpoons C$ kinetic situation. The exact solutions for that case are known,⁹ but obtaining the numerical values of the rate constants required a computer solution. The program devised¹⁰ utilized concentration I vs. time data to provide rate constants for the four reactions involved in $I \rightleftharpoons II \rightleftharpoons III$. The set of k 's which provided calculated concentration I vs. time data with minimum standard deviation from the experimental data was taken as a measure of the accuracy of the rate constants. Figure 1 gives, graphically, an example of the results of computer calculations for the rearrangement of I at 235° . The rate constants at three temperatures are listed in Table I (runs 4, 8, and 9).

As a check on the role of hydroxyimine II as an intermediate in the rearrangement, pure II was subjected to rearrangement conditions and the appearance of amino ketone I was followed by ultraviolet spectra. These data were subjected to analysis by the same computer program and the results are tabulated in Table I (run 10). This experiment also served as a reproducibility check. Thermodynamic constants were calculated at all temperatures for five of the six reactions involved in the I-IV sequence. These were averaged and are presented in Table II.

Table II. Activation Constants of the α -Amino Ketone Rearrangement

Rate constant	E_a , kcal mole ^{-1a}	ΔH^\ddagger , kcal mole ⁻¹	ΔS^\ddagger , eu	ΔG^\ddagger_{190} , kcal mole	σ , % ^b
k_1	25.8	24.9	-23.6	35.8	2
k_2	22.3	21.4	-29.4	35.0	10
k_3	17.5	16.6	-43.4	36.7	14
k_4	18.6	17.6	-43.1	37.6	<i>c</i>
k_5^d	35.1	34.2	-1.9	35.1	20

^a Calculated from least-squares slope of an Arrhenius plot. ^b Standard deviation of three values of E_a from the least-squares line. ^c Values of k_4 are approximations. The k_4 at 174° was not used and E_a was calculated from the integrated Arrhenius equation rather than from the slope. The deviation in this E_a is the highest of all. ^d Enthalpy and entropy values mentioned previously²⁸ are the result of a calculation error.

(9) T. M. Lowry and W. T. Jones, *J. Chem. Soc.*, 97, 2634 (1910).

(10) The authors are indebted to Professor Stanley K. Stynes and Mr. Ray Hunter of the College of Engineering, Wayne State University, for developing the computer program. A brief description of the program is presented in the Experimental Section. Complete details will shortly be published elsewhere.

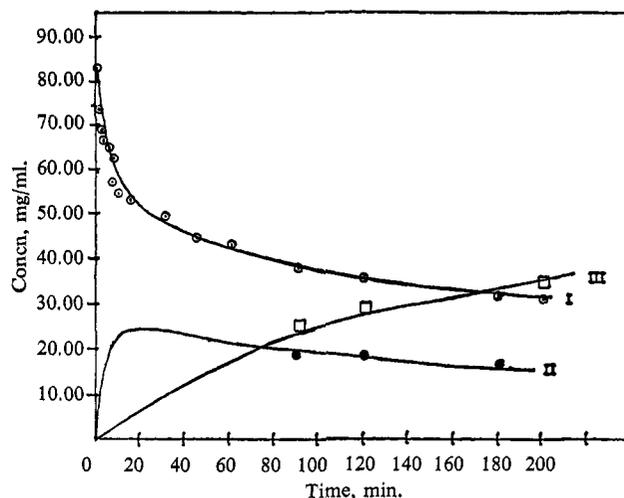


Figure 1. Concentration vs. time plot of the rearrangement of I at 235° . The solid lines are concn vs. time data calculated by computer. Circles are experimental [I] vs. time; squares are experimental [III] vs. time (by infrared); solid dots are experimental [I] - experimental [III].

Discussion

IV-III. The most striking property of the rearrangement is the ΔS^\ddagger which is considerably higher than the -15 to -10 eu usually observed for unimolecular rearrangements. However, the infrared spectrum of IV in chloroform revealed a strongly hydrogen bonded hydroxyl absorption at 2135 cm^{-1} (chelate region $3200\text{--}2500 \text{ cm}^{-1}$)¹¹ which was not affected by concentration changes. Thus, the indicated strong $\text{N} \cdots \text{H}-\text{O}$ hydrogen bond¹² would dictate the highly ordered and polar ground state pictured in Scheme I for IV, a situation which would afford a minimum loss in entropy on proceeding from IV to (III-IV)* (Scheme I). Change to the more polar solvent *o*-dichlorobenzene accelerated the rearrangement by a factor of about 2 (compare runs 6 and 7, Table I) perhaps in part by facilitating polarization of the $>\text{C}=\text{N}-$ group. Acid catalysis should also facilitate such polarization, and, indeed, the acid salts of IV and analogous imines undergo faster rearrangements than their free bases.¹³ The irreversible nature of $\text{IV} \rightarrow \text{III}$ (estimated $\Delta F^{235} = -4.6$ kcal) probably arises from the roughly $5\text{--}18$ -kcal energy difference¹⁴ between the systems $\text{C}=\text{N} + \text{C}-\text{O}-\text{H}$ and $\text{C}=\text{O} + \text{C}-\text{N}-\text{H}$. These present data now complement previously presented studies²⁸ of the rearrangement of α -hydroxy-N-phenylimines.

I-II-III. For devising the computer program it was necessary, initially, to assume that the reactions to be studied were, indeed, all first order. However, it could be shown, in general, that if the disappearance of I were a second-order reaction (rate = $k[\text{I}]^2$) the program would have yielded calculated data which would not have satisfied both the experimental data and an Arrhenius plot. The rate constants calculated from this

(11) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1958, p 95. Also K. Nakanishi, "Infrared Absorption Spectroscopy," Holden-Day, Inc., San Francisco, Calif., 1962, p 30.

(12) Imine IV is quite basic: $\text{p}K_a' = 6.7$ (50% methanol).

(13) More details and the synthetic utility of such acid catalysis will be presented elsewhere.^{1,20,d}

(14) Estimated from bond energy values found in C. R. Noller, "Chemistry of Organic Compounds," 3rd ed, W. B. Saunders Co., Philadelphia, Pa., 1965, p 993.

program generated [I] vs. t curves almost indistinguishable from the experimental data at all three temperatures used and the fits of k_1 , k_2 , and k_3 to an Arrhenius plot were all good (cf. Table II, σE_a values). A test of the reaction order by changing the starting concentration of I (and necessarily II) was accomplished in the kinetic run where II was the starting material (Table I, run 10). From these data it can be concluded that the reactions being examined are first order.¹⁵

However, the rate constants observed for I-IV could contain a factor which is a function of the total concentration of all reactants and which would, consequently, be a constant. Indeed, preliminary studies on concentration effects in the analogous N-phenyl series have indicated that the rate of rearrangement of IV (N-*p*-anisyl) in decalin is enhanced by higher starting concentrations, but that in a given run no systematic drift of calculated first-order k 's results.^{3b} The solvents for these rearrangements are hydrocarbons and dissolution of solutes such as compounds IV (*n*-phenyl) must sharply raise the dielectric constant and polarity of the reaction medium. Such increase in the dielectric constant would be expected to increase the rate of rearrangement, since it has been noted that use of *o*-dichlorobenzene (dielectric constant 9.9) enhanced the rearrangement of IV. Therefore, it would also be expected that the I-IV rearrangement, while exhibiting good first-order kinetics, should show rates enhanced by increases in starting concentration and solvent dielectric constant. Further work along these lines is in progress.

In consideration of the calculated ΔS^* ¹⁶ values only as ΔS^* trends it is found that the trends observed are quite reasonable. Thus, the hydrogen bonded ground state of IV permits a ring expansion with a more favorable ΔS^* than the analogous reaction in non-hydrogen bonded I. Further, a weakly hydrogen bonded ground state compared to IV is indicated for II ($\nu_{\text{-OH}}$ 3280 cm^{-1}). The higher basicity of imine II ($\text{p}K_a' = 7.8$) compared to IV,¹² and the weaker hydrogen bond in II, are taken as evidence for the greater N...H—O distance that would be dictated by an equatorial phenyl group. Conversion of II to III requires that the phenyl group become axial (II \rightarrow II') from whence it can migrate *via* (II-III)* to yield III. Conversion of an equatorial to an axial phenyl is expected to proceed with some loss in entropy.¹⁷ Passage to the highly rigid transition state, (II-III)*, in which phenyl rotation is completely halted and the six-membered ring supports fused five- and three-membered bridges, would be expected to exhibit a rather unfavorable ΔS^* . The competing reversal of this reaction, II \rightarrow I, would not appear to possess such unfavorable entropy requirements. Thus it is seen that the ring contraction can proceed from II with phenyl equatorial, that phenyl rotation need not be halted in (I-II)*, and the bridging requirements for

(I-II)* are less. Therefore, the ΔS^* requirements for I-II would be expected to be less than for II-III and this is what is observed.

Since the trends shown by ΔS^* appear to be reasonable, their magnitudes can be viewed with more confidence. It is well known that nonpolar solvents accentuate unfavorable ΔS^* effects for charge separation in a transition state.^{16, 18} This is no doubt the case here and these effects might be expected to be accentuated further if relatively polar *solute* molecules are solvating the transition state. A phenomenon such as this would also be consistent with the observed rate enhancements due to higher starting reactant concentration¹⁹ and higher solvent dielectric constant.

In summary the amino ketone rearrangement is envisioned as proceeding as pictorially described in Scheme I. Thus, IV rearranges to the more thermodynamically stable III with a minimum of orientation and charge-distribution change on going to the transition state (III-IV)*.²⁰ Further, I and II interconvert with roughly comparable requirements, while the II-III interconversion appears to be an entropy-controlled reaction in these solvents.

Experimental Section

Melting points are uncorrected and were obtained on a Thomas-Hoover capillary melting point apparatus. Elemental analyses were done by Midwest Microlab, Inc. Infrared spectra were obtained on a Beckman IR-4 and ultraviolet spectra were obtained on a Cary 14. All $\text{p}K_a$'s were obtained in 50% methanol on the automatic titrimeter previously described.²¹

All samples of methylamine were distilled through a drying tower of reagent grade potassium hydroxide. The hydrocarbon solvent used were the commercially available high purity compounds which were redistilled from calcium hydride. The *o*-dichlorobenzene used was dried overnight over anhydrous potassium carbonate and then fractionally distilled.

Standard Rearrangement Conditions. The compound studied was heated near solvent reflux under a constant flow of dried helium gas in a flask fitted with thermometer well, condenser, helium inlet, and stoppered sampling arm. Solid compounds were dissolved in the given solvent and the reaction vessel was lowered into a Wood's metal bath which had been preheated. Liquid compounds were injected by syringe into solvent which had already been brought to the appropriate temperature.

Demonstration of 2-Hydroxy-2-phenylcyclohexanone-N-methylimine in a Rearrangement. In preheated tridecane (30 ml) under the usual rearrangement conditions, 2.0 g (0.0098 mole) of I was heated at 235° for 12 min and then rapidly cooled. The reaction solution was then poured into 150 ml of 2-propanol and treated with excess sodium borohydride (3 g), and the mixture was refluxed overnight. The basic fraction was isolated and spotted in thin layer chromatography (acetone) and showed the three spots of VI (R_f 0.37), and IX (R_f 0.21). The mixture was then separated by preparative thin layer chromatography using 200 \times 200 mm plates with Silica Gel H coating 0.500 mm thick. This yielded 300 mg (38%) of IX isolated as its hydrochloride salt (yield corrected for the fact that $1/3$ of the basics was used) and 250 mg of VI (16% corrected for the fact that $2/3$ of the basic was used) also isolated as its hydrochloride. Both the hydrochlorides were identified by mixture melting points with authentic samples.

(18) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Co., New York, N. Y., 1959, p 182.

(19) Such effects have been seen in nonunimolecular reactions involving ions: C. G. Swain, *J. Am. Chem. Soc.*, **70**, 1119 (1948); L. C. King and D. L. Breber, *ibid.*, **75**, 2330 (1953).

(20) It is tempting, therefore, to attribute the ΔS^* of the sterically similar I-II rearrangement largely to charge separation in (I-II)*. Further, since the degree of charge separation for (I-II)* and (II-III)* might be expected to be similar, ~ 20 eu of the ΔS^* of the II-III rearrangement can be accounted for in that manner, leaving a ~ 20 -eu requirement for the double bridging.

(21) A. M. Wilson and M. E. Munk, *Anal. Chem.*, **25**, 407 (1953).

(15) It can be added that any second-order pathway requires intermolecular proton transfers which, for all four reactions, can occur intramolecularly *via* five-membered rings.

(16) The values of ΔS^* fall into the range usually seen for second-order reactions: J. Leffler, *J. Org. Chem.*, **20**, 1202 (1955).

(17) Calculations have indicated that axial ethyl and isopropyl groups experience restricted rotation relative to their equatorial counterparts and thus have less entropy: E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," John Wiley and Sons, Inc., New York, N. Y., 1965, p 60. An analogous situation is expected to prevail for the phenyl case.

Thermal Rearrangement of 2-Hydroxy-2-phenylcyclohexanone-N-methylimine (II). In 20 ml of redistilled *n*-tridecane which had been preheated to 230°, II (1.11 g, 0.00546 mole) was refluxed at 235° for 3 hr. The reaction mixture was then added to 100 ml of 2 *N* hydrochloric acid, stirred vigorously overnight, and then heated for 1 hr on a steam bath. The basics were isolated and chromatographed over Florisil. Elution with hexane-ether (4:1) gave amino ketone I which was isolated as its hydrochloride (310 mg, 23.7%, mp 114–116°, mixture melting point with authentic sample undepressed). Further elution with hexane-acetone (1:1) gave amino ketone III isolated as its hydrochloride (670 mg, 51.1%, mp 259–261°, mixture melting point undepressed).

Thermal Reversal of Amino Ketone III. In 10.0 ml of *n*-tridecane was dissolved III^{2a} (950 mg, 0.0047 mole) and the solution was heated under rearrangement conditions at 236°. After 3 hr, an aliquot was taken and its infrared spectrum was determined neat. In this spectrum was seen a strong absorption at 1740 cm⁻¹ (starting material), a well-resolved medium strength absorption at 1680 cm⁻¹ (conjugated ketone or unconjugated imine). No absorption at 1650 cm⁻¹ (conjugated C=N) could be seen. The reaction solution was spotted in thin layer chromatography (methyl ethyl ketone-methyl isopropyl ketone-ligroin (90–91°), 6:3:1) revealing clear spots at *R_f* 0.24, 0.51, and 0.69, identified as II, I, and III, respectively, by comparison with standard samples. Spots at the origin and solvent front were also seen. In order to get a clean pattern of spots, it was found necessary to bake the plates at 110° for 15–20 min before running to remove the tridecane. If the plates were not so treated, only a long streak was obtained. The known samples were likewise treated without ill effect. The minimum detectable concentration of IV was obtained by calculating the low concentration extinction coefficient for the C=N absorption at 1650 cm⁻¹ from a known rearrangement spectrum with a low concentration of IV and then calculating the per cent of IV required to show the detectable change of 19% transmittance.

A second aliquot was taken after 7 hr, but by this time the reaction had turned dark brown and showed marked visible evidence of decomposition. Infrared showed no significant change in the carbonyl region from that obtained after 3 hr.

Mass Balance in the Thermal Rearrangement of I. Under the usual rearrangement conditions, I (1.8 g, 0.088 mole) was heated at 235° for 2.5 hr in tridecane. The reaction solution was allowed to cool to room temperature and then poured into 150 ml of 2-propanol. Sodium borohydride (3 g) was then added and the mixture refluxed overnight. The usual work-up yielded 1.88 g of basic material which when spotted in thin layer chromatography (system B) showed three spots at *R_f* 0.21, 0.37, and 0.51 corresponding to IX, VIII, and VI. There was also a slight trace of material which ran with the solvent front. After spotting, the basics were dissolved in acetone and treated with excess 2-propanol saturated with hydrogen chloride. The mixture of hydrochlorides was obtained as a colorless crystalline mass weighing 2.4 g (95%).

Kinetics of the Rearrangement of IV–III. In the designated solvent, a weighed amount of hydroxyimine IV was rearranged under standard condition. At the indicated times, 1-ml aliquots were removed by hypodermic syringe. Starting concentrations ranged between 72 and 94 mg/ml. The aliquots (between 6 and 10 were taken) were directly placed in an infrared spectrophotometer cell and their infrared absorption at 1740 cm⁻¹ determined against a pure rearrangement solvent blank. Interspersed with the experimental samples were samples of weighed III. The base line of the instrument was set by running solvent *vs.* solvent. Even in the case of *o*-dichlorobenzene, a straight base line was obtained in the region of interest. Concentrations of product were determined by constructing a calibration curve from the known samples. Table III presents representative data.²²

Kinetics of the Rearrangement of I. Using the same conditions and methods of sample removal given for the rearrangement of IV, the thermal rearrangement of amino ketone I^{2a} was studied. The aliquots removed were measured in a μ l pipet into 100-ml volumetric flasks and diluted with absolute ethanol. Ultraviolet spectra were then obtained and compared with standards of the ultraviolet spectra of the starting material (λ_{\max} (ethanol) 247 μ m (ϵ 9850)). Starting concentrations ranged between 72 and 100 mg/ml and 14–17 aliquots were taken. An ultraviolet spectrum of 50 μ l of tridecane in ethanol *vs.* ethanol showed no change in the base line, thus eliminating any interference of the hydrocarbon solvent. Representative data is presented in Table III.²²

Table III. Concentration *vs.* Time Data for I–IV Rearrangement

A. III–IV, 184° in Decalin					
Time, min	Concn, mg/ml	Time, min	Concn, mg/ml	Time, min	Concn, mg/ml
0	86.0	33	66.0	60	55.0
10	80.0	45	61.0	85	44.0
20	75.0	51	59.0	105	37.0
B. I–II–III, 235°, Tridecane					
Time, min	Concn of I, mg/ml	Time, min	Concn of I, mg/ml	Time, min	Concn of I, mg/ml
0.0	82.75	15	53.5		
2	71.9	30	50.0		
3	68.0	45	46.0		
4	65.0	60	44.0		
5	63.0	90	39.5		
7	60.5	120	36.5		
8	56.5	180	32.7		
10	54.5				

In the rearrangement at 235° the infrared technique used for the rearrangement of IV was attempted, but it was found that the infrared absorption of the starting material was too close to that of final product to give an interference-free spectrum. Since standardization would have required the preparation of three-component mixtures, the infrared analysis was not used to any great extent. One attempt did give reasonable agreement with the calculated concentration *vs.* time curve (*cf.* Figure 1).

Kinetics of the Rearrangement of Hydroxyimine II. The procedure for the rearrangement of I was adapted for the case of II. The starting concentration of II was 79.7 mg/ml and the temperature was 235° in tridecane.²²

1-(α -Methyliminobenzyl)cyclopentanol (IV). α -Bromocyclopentyl phenyl ketone^{2a} (16.0 g, 0.063 mole) was dissolved in 150 ml of distilled anhydrous methylamine and the mixture stirred overnight, during which time the methylamine slowly evaporated. The last traces of methylamine were removed *in vacuo* and the resulting solid was triturated with anhydrous ethyl ether. The methylamine hydrobromide was removed by filtration of the ether solution and the ether was removed *in vacuo*. Hydroxyimine IV, 12.2 g (96%), mp 74°, was obtained as white crystals by crystallization from hexane, infrared (ν_{CHCl_3}) 1650 cm⁻¹, $\text{p}K_{\text{a}}' = 6.7$.

Anal. Calcd for C₁₃H₁₇NO: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.73; H, 8.47; N, 6.87.

A reduction product was prepared in 80% yield by sodium borohydride reduction at room temperature in methanol. The resulting amino alcohol was isolated as its hydrochloride salt, mp 174–175° after recrystallization from ethanol-pentane.

Anal. Calcd for C₁₃H₂₀ClNO: C, 64.60; H, 8.28; N, 5.80. Found: C, 64.20; H, 8.34; N, 5.80.

Thermal Rearrangement of IV. A Preparation of Amino Ketone III. In 46.0 ml of redistilled *o*-dichlorobenzene under the kinetic rearrangement conditions, IV (4.30 g, 0.21 mole) was rearranged to yield 2-methylamino-2-phenylcyclohexanone (III) which was isolated as its hydrochloride salt, 3.55 g (70.2%), mixture melting point with an authentic sample^{2a} undepressed, 256–258°. During reaction 12.0 ml of reaction solution (26.1%) was removed for infrared analysis to determine the end of the reaction (2 hr). Hence the mass balance obtained was 96.3%.

2-Hydroxy-2-phenylcyclohexanone-N-methylimine (II). In a sealed tube were placed 2-hydroxy-2-phenylcyclohexanone⁴ (4.5 g, 0.0236 mole), redistilled methylamine (25 ml), and anhydrous potassium carbonate (1 g). The tube was allowed to stand in the dark at room temperature for 5 days. All material was then washed from the tube with anhydrous ethyl ether and all volatile products were distilled *in vacuo*. The residue was then redissolved in ether and filtered to remove potassium carbonate, and the ether once again was removed *in vacuo*. The residue was vacuum distilled to yield II, 3.97 g (83%), bp 75° (0.05 mm), $n_{\text{D}}^{25} 1.5513$, as a highly unstable light yellow oil. Infrared (ν_{CHCl_3}) 3280 and 1680 cm⁻¹. Upon standing in a freezer, the oil solidified to material mp 35–40°. However, all attempts to recrystallize this solid gave either gums or a new material with a wide melting range and an infrared spectrum different from that of II.

Anal. Calcd for C₁₃H₁₇NO: C, 76.80; H, 8.43; N, 6.89; O, 7.87. Found: C, 76.65; H, 8.32; N, 6.86; O, 8.87.

(22) Complete data can be made available on request.

Treatment of this imine in chloroform with an anhydrous toluene solution of *p*-toluenesulfonic acid yielded quantitatively the acid salt upon addition of anhydrous ethyl ether, mp 131–133°. It was found that all attempts to recrystallize this salt yielded material which was at least partially hydrolyzed and analysis was obtained on the crude material; the pK_a' was 7.83.

Anal. Calcd for $C_{20}H_{28}NO_4S$: C, 63.97; H, 6.70; N, 3.73. Found: C, 63.69; H, 6.70; N, 3.78.

trans-2-Methylamino-2-phenylcyclohexanol (VIII). 2-Methylamino-2-phenylcyclohexanone hydrochloride (3.600 g, 0.015 mole) was dissolved in 150 ml of methanol and 3.6 g (0.095 mole) of sodium borohydride was slowly added over a 30-min period while the solution was stirred. The reaction mixture, protected with a Drierite drying tube, was allowed to stir overnight at room temperature. Then 50 ml of 6 *N* hydrochloric acid was added slowly with continued stirring. The entire mixture was then evacuated to dryness, the residue taken up in 50 ml of water, and potassium hydroxide added until a pH of 12 was reached. The alkaline solution was extracted with three 50-ml portions of chloroform, the chloroform dried over potassium carbonate, and the solvent removed *in vacuo*. The resulting solid was chromatographed over 100 g of neutral (grade III) alumina. Elution with hexane gave 2.42 g (80%), mp 93–95°, of VIII. The compound sublimed quantitatively for analysis.

Anal. Calcd for $C_{13}H_{19}NO$: C, 76.05; H, 9.33; N, 6.82. Found: C, 76.01; H, 9.49; N, 6.60.

A hydrochloride salt was prepared, mp 238–240°; the pK_a' was 8.5.

Anal. Calcd for $C_{13}H_{20}ClNO$: C, 64.58; H, 8.34; Cl, 14.66; N, 5.80. Found: C, 64.42; H, 8.49; Cl, 14.71; N, 5.79.

α -(1-Cyclopentyl-1-methylamino)benzyl Alcohol (IX). By the reduction procedure described for the preparation of VIII, amino ketone I was converted to alcohol IX in 62% yield, mp 85–86° after recrystallization from hexane; the pK_a' was 9.62.

Anal. Calcd for $C_{13}H_{19}NO$: C, 76.05; H, 9.33; N, 6.82. Found: C, 76.19; H, 9.45; N, 6.58.

The hydrochloride salt was prepared and had mp 235–237° after recrystallization from ethanol-ether.

Anal. Calcd for $C_{13}H_{20}ClNO$: C, 64.58; H, 8.34; N, 5.80. Found: C, 64.66; H, 8.38; N, 5.57.

trans-1-Phenyl-2-methylaminocyclohexanol (VI). Using the procedure of VIII, amino alcohol VI was prepared in 77% yield, mp 135–136° after recrystallization from ether; the pK_a' was 8.60.

Anal. Calcd for $C_{13}H_{19}NO$: C, 76.05; H, 9.33; N, 6.82. Found: C, 75.86; H, 9.39; N, 6.97.

The hydrochloride salt melted at 219–221° after recrystallization from ethanol-ether.

Anal. Calcd for $C_{13}H_{20}ClNO$: C, 64.58; H, 8.34; N, 5.80. Found: C, 64.84; H, 8.33; N, 5.64.

trans-1-Phenyl-2-N,N-dimethylaminocyclohexanol. In a solution of 20 ml of 90% formic acid and 8 ml of 33% formaldehyde amino alcohol VI (1.4 g, 0.0068 mole) was refluxed for 8 hr. The solution was treated with 10 ml of 3 *N* hydrochloric acid and all solvents were removed *in vacuo*. The residue was dissolved in 50 ml of 2 *N* hydrochloric acid and extracted twice with 50-ml portions of ethyl ether. The pH of the aqueous layer was raised to 12 with potassium hydroxide and extracted twice with 100-ml portions of ethyl ether. The ether extracts so obtained were dried over anhydrous potassium carbonate and the ether extracts reduced to 50 ml *in vacuo*. Upon treatment with 2-propanol-hydrogen chloride, *trans*-1-phenyl-2-N,N-dimethylaminocyclohexanol hydrochloride was obtained, 1.16 g (67%), mp 204–206°; the pK_a' was 9.3.

Anal. Calcd for $C_{14}H_{22}ClNO$: C, 65.73; H, 8.67; Cl, 13.86; N, 5.48. Found: C, 65.51; H, 8.80; Cl, 13.95; N, 5.45.

trans-1-Phenyl-2-(N,N,N-trimethylammonium Iodide)-Cyclohexanol (VII). For 10 min on a steam bath under a Drierite-protected water condenser, *trans*-1-phenyl-2-N,N-dimethylaminocyclohexanol (0.500 g, 0.00023 mole) was refluxed with 20 ml of methyl iodide and 5 ml of methanol. Upon cooling and the slow addition of anhydrous ethyl ether, the quaternary ammonium salt crystallized, 0.550 g (78%), mp 212–214°.

Anal. Calcd for $C_{13}H_{24}INO$: C, 49.87; H, 6.70; I, 35.13; N, 3.88. Found: C, 50.10; H, 6.86; I, 35.01; N, 3.96.

1-Phenylcyclohexene Oxide and *cis*-2-Phenyl-2-hydroxycyclohexanol from VII. Sodium hydroxide (0.40 g, 0.01 mole) and silver nitrate (0.75 g, 0.0045 mole) were mixed in 20 ml of distilled water, forming silver oxide as a dark brown precipitate. To this mixture was added VII (1.3 g, 0.0036 mole) in 65 ml of absolute ethanol. The resulting mixture was shaken manually for 25 min. At the end of this time the color of the precipitate had essentially

changed from dark brown to brownish yellow. All solids were removed by filtration and the filtrate extracted with three 50-ml portions of petroleum ether (bp 30–60°). Another 50-ml portion of petroleum ether was used to carefully wash the collected solids. All the petroleum ether portions were combined and dried over anhydrous potassium carbonate, and the solvent was removed *in vacuo* yielding a clear, colorless oil which was distilled (evaporatory distillation at 60–65° (0.05 mm)) to yield 600 mg (96%) of 1-phenylcyclohexene oxide,⁶ identified by its infrared spectrum which showed no absorptions at 2.8–3.2 or at 5.5–6.1 μ and which was virtually superimposable with that of an authentic sample prepared by epoxidation of 1-phenylcyclohexene with *m*-chloroperbenzoic acid. The oil was hydrolyzed by refluxing it in distilled water overnight affording in 51% yield the known *cis*-1-phenyl-2-hydroxycyclohexanol as evidenced by an undepressed mixture melting point with an authentic sample (all 90–92°).⁷

Preliminary Work on Concentration Effects. Weighed samples of 1-(α -*p*-methoxyphenyliminobenzyl)cyclopentanol²⁸ (the *N*-*p*-anisyl analog of IV) were dissolved in decalin, sealed in flasks, and heated at 208° for 1 hr. The decalin was evaporated *in vacuo*, the samples were dissolved and made up into appropriate volumes of chloroform, and their infrared spectra were taken. Using the procedure previously described²⁸ the concentration of starting imine was determined. The results are tabulated in Table IV.

Table IV

Sample	Initial concn, mg/ml	Concn (1 hr), mg/ml	$\sim k \times 10^5$ sec ⁻¹
1	12.0	8.3	4
2	30.0	19.5	5
3	60.0	32.7	7
4	120	54	10

The Computer Program.¹⁰ The derivation of the formulas proceeded through six steps; the first step is the presentation of the rate equations for the situation $I \rightleftharpoons II \rightleftharpoons III$ where each reaction is first order, and the rate constants are k_1 , k_2 and k_3 , k_4 , respectively. In the second step the Laplace transformation is applied to formulate a system of algebraic equations. In the third step the system is solved for I, II, and III in terms of the Laplace variable by employing determinants. The inverse Laplace transform is used to reintroduce the time variable. The fifth step summarizes the equations and affords solutions for (I)_t, etc. which are in agreement with the previous report.⁹ The sixth and final step is the calculation of the partial derivatives $\partial(I)_t/\partial k_i$ where i equals 1, 2, 3, and 4.

The derivation is quite general in that it applies to the described situation given any values of (I)₀, (II)₀, and/or (III)₀. It applies to any simplified situation if the proper $k(s)$ is set equal to zero and the directional nomenclature is maintained as long as k_1 is not zero. Thus the partials can be employed for $I \rightarrow II \rightarrow III$; $I \rightarrow II \rightleftharpoons III$; $I \rightleftharpoons II \rightarrow III$; $I \rightleftharpoons II$, etc., but not for $I \leftarrow II \rightarrow III$.

The derivation is applicable to determinations of rate constants using (I)_t vs. t data; (II)_t vs. t data; or (III)_t vs. t data or a combination of such data. Equilibrium concentrations are not required and can, of course, be calculated from the rate constants.

The program employed for this study was one which calculated the desired rate constants using only (I)_t vs. time data and the total initial concentrations, C_0 . The reactants could have been present in any concentrations but as used C_0 equalled either (I)₀ or (II)₀.

The program performs a gradient-search modification of the method of steepest descent to find a set of rate constants that will provide the best fit to the experimental data of the data calculated from the mathematical model. The measure of this best fit is the standard deviation of the values of (I)_t calculated from the experimental values.

Two limitations exist for the program-computer combination used. They are that the program cannot use sets of experimental data containing more than 50 data points, and it cannot find k values of less than 10^{-10} . The former limitation could be easily removed if necessary.

The computer used was an IBM 7074.

Acknowledgment. Generous support from the National Science Foundation (Grant GP-205) is gratefully acknowledged.