The Beckmann Rearrangement of the Geometrical Isomers of Cyclohexyl Phenyl Ketoxime in Liquid Sulfur Dioxide[1]

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In the previous report[1] of this series some effects of reagents on the products of the Beckmann rearrangement have been reported. It is currently accepted[2] that the Beckmann rearrangement is accompanied by exclusive trans migration. However, Some anomalies on the migratory aptitude in this rearrangement have been observed. Recently, Brown, van Gulic and Schmid[3] have reported that when pivalophenoxime was subjected to the Beckmann rearrangement with hydrochloric acid in acetic acid, similar products were obtained either from the *syn*-oxime or from the *anti*-isomer. This phenomena could be accounted for by a preliminary isomerization of the oximes before the rearrangement. On the other hand, Yukawa, Hanabusa and Kin[4] have examined the Beckmann rearrangement of cyclohexyl phenyl ketoximes and found that the migratory aptitude varied according to the reagents applied.

In addition, in the light of the publications hitherto reported[5-7], the geometrical structures of the cyclohexyl phenyl ketoximes are still ambiguous. Contradictory geometrical structures have been assigned to the oximes by Meyer and Scharvin[5,6] and also by Meisenheimer and Theilacher[7]. Moreover, since its first synthesis in 1897 by Meyer and Scharvin[5], the establishment of the geometrical structures mainly depended upon the analysis of the migrated products of the Beckmann rearrangement and the above-mentioned random migratory aptitude was ignored.

It is the purpose of the present writers to carry out the rearrangement in liquid sulfur dioxide of this compound to obtain further information on the geometrical structures of this ketoxime and the migration tendency in the Beckmann rearrangement by subjecting it to a more moderate condition. The isomeric cyclohexyl phenyl ketoximes were prepared and separated by the well-known precedure[5], to give the α-oxime, m. p. 156∼157°C., and β-oxime, m. p. 113∼114°C, respectively after repeated fractional precipitations from acetic acid solution by the addition of water.

The authentic specimens of the acid amides,

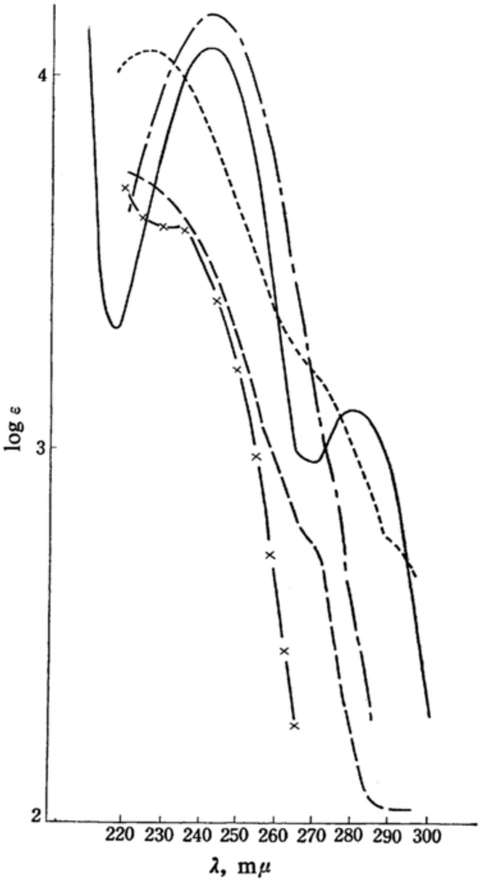

Fig. 1. Ultraviolet absorption spectra of cyclohexyl phenyl ketoximes and the derived acid amides.

- ---- α-Cyclohexyl phenyl ketoxime (I)
- -×- β-Cyclohexyl phenyl ketoxime (II)
- ------ *N*-Cyclohexyl benzamide (III)
- —-— Cyclohexanecarboxyanilide (IV)
- —— Cyclohexyl phenyl ketone (V)

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[1] Part VI; On the Beckmann rearrangement in liquid sulfur dioxide. Previous papers on this series: IV. R. Tada, H. Sakuraba and N. Tokura, This Bulletin, **31**, 1003 (1958). V. N. Tokura, R. Tada and H. Suzuki, ibid., **32**, 654 (1959).

[2] B. Jones, *Chem. Revs.*, **23**, 335 (1944).

[3] R. F. Brown, M. M. van Gulic and G. H. Schmid, *J. Am. Chem. Soc.*, **77**, 1094 (1955).

[4] Y. Yukawa, "Jikken Kagaku Koza", Vol. 18, Maruzen Co. Ltd., Tokyo, (1957), p. 426.

[5] V. Meyer and W. Scharvin, *Ber.*, **30**, 1942 (1897).

[6] W. Scharvin, ibid., **30**, 2862 (1897).

[7] J. Meisenheimer and W. Theilacher, "Stereochemie", edited by Freudenberg Leibzig (1933), p. 2103.

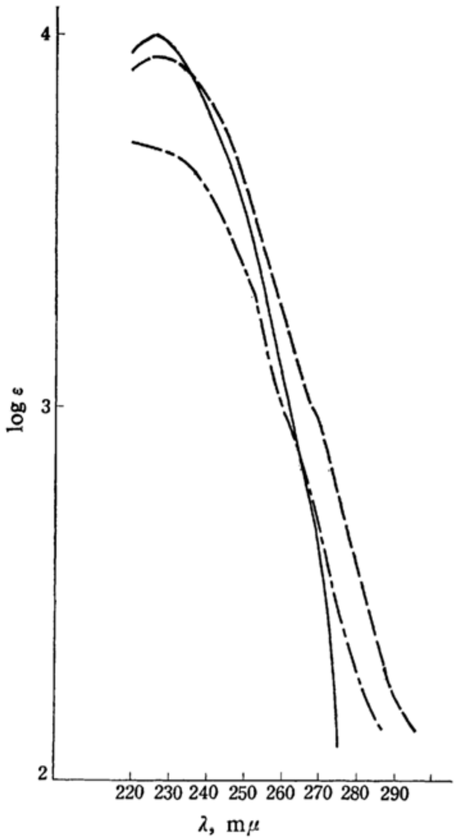

Fig. 2. Ultraviolet spectra of the reaction products from α-oxime I in liquid SO_2 at −70°C.

—— $SOCl_2$
–-– $SOCl_2$ in ether
---- Bromine

which should be expected to produce by the Beckmann rearrangement from the ketoximes, *N*-cyclohexyl benzamide (III), m. p. 148∼149°C (reportedly[8] 146°C) and cyclohexanecarboxyanilide (IV), m. p. 146.5∼147°C (reportedly 139°C)[9] respectively, were also prepared for identification of the reaction product and the ultraviolet spectra of the respective amides were compared. Although the melting point of the two compounds were close to each other, the mixed melting point of the two authentic acid amides, III and IV, was depressed to 112∼116°C.

A preliminary test was performed to confirm the stability of the oximes in liquid sulfur dioxide. In the range of this experimental condition the α-oxime was sufficiently stable whereas the β-oxime isomerized to the α-oxime gradually in liquid sulfur dioxide. Accordingly, special attention was paid to carry out the Beckmann rearrangement of the β-oxime.

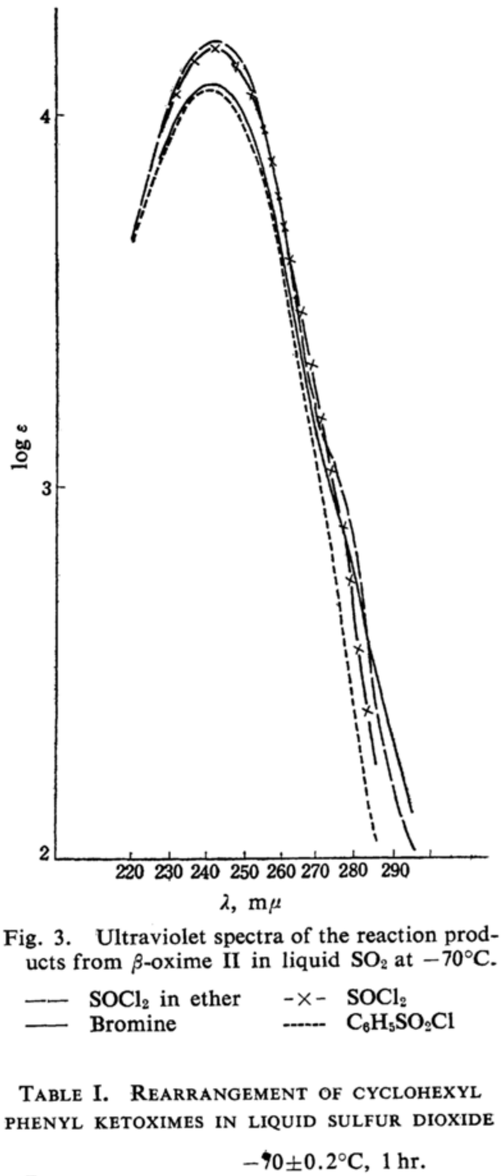

Fig. 3. Ultraviolet spectra of the reaction products from β-oxime II in liquid SO_2 at −70°C.

–-– $SOCl_2$ in ether -×- $SOCl_2$
—— Bromine ------ $C_6H_5SO_2Cl$

TABLE I. REARRANGEMENT OF CYCLOHEXYL PHENYL KETOXIMES IN LIQUID SULFUR DIOXIDE

Reagent	−70±0.2°C, 1 hr.	
	Product	Rearrangement
α-Oxime I		
$SOCl_2$	III	trans
$C_6H_5SO_2Cl$	I	No
Bromine	III	trans
HCl	I	No
HBr	I	No
$SOCl_2$ in ether	I	No
β-Oxime II		
$SOCl_2$	IV	trans
$C_6H_5SO_2Cl$	IV	trans
Bromine	IV	trans
HCl	I+V	No, deoximation
HBr	I+V	No, deoximation
$SOCl_2$ in ether	IV	trans

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[8] W. Markownikoff, *J. Chem. Soc.*, **87**, 92 (1892).
[9] J. S. Lumsden, *Ann.*, **302**, 27 (1905).

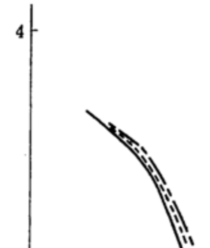


Fig. 4. Ultraviolet spectra of the reaction products from α-oxime I by hydrogen halides in liquid SO_2 at −70°C.
---- HCl —— HBr
—-— α-Oxime (I)

The Beckmann rearrangement were carried out in liquid sulfur dioxide at −70°C to avoid any undesirable side reaction. The reagents adopted for the rearrangement were thionyl chloride, benzenesulfonyl chloride, bromine and hydrogen halides. The result of the rearrangement is listed in Table I.

When the Beckmann rearrangement was carried out with thionyl chloride at −70°C in liquid sulfur dioxide, neither the α-oxime nor the β-oxime showed the random migratory aptitude, affording only *N*-cyclohexyl benzamide(III) from α-oxime I, and cyclohexanecarboxyanilide (IV) from β-oxime II, respectively. The mixed melting point and the superimposability of the ultraviolet spectra with those of the authentic specimen have proved that the rearrangement was progressing only in one direction, producing a single acid amide of the two.

The similar results were also obtained by other reagents, by which the different migratory aptitudes were not displayed in the rearrangements.

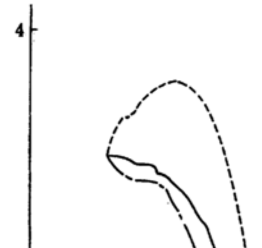
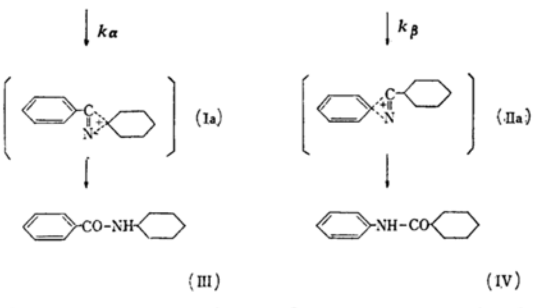


Fig. 5. Ultraviolet spectra of the reaction products from β-oxime II in liquid SO_2 at −70°C.
---- HCl —— HBr
—-— β-oxime (II)

Chart 1.

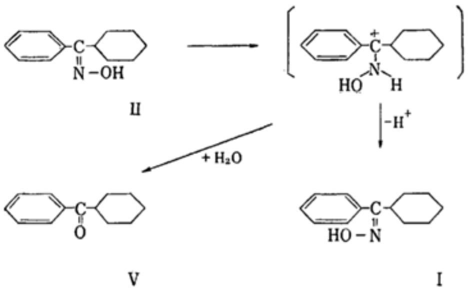


Thus, among a variety of reagents examined, within the range of these experimental conditions, thionyl chloride and bromine were only effective for the rearrangement of the α-oxime, from which both reagents yielded the compound III exclusively as the result of trans migration.

As for the less stable β-oxime, the rearrangements were effected by thionyl chloride, benzenesulfonyl chloride and bromine to yield the amide IV exclusively, again the trans migration being predominant.

Hydrogen chloride and hydrogen bromide were both ineffective for the rearrangement, recovering the original α-oxime when it was started from the α-oxime or yielding a mixture of cyclohexyl phenyl ketoxime (V) and the α-oxime isomerized when the β-oxime was reacted. It is not surprising that the β-oxime unreacted was transformed to the more stable α-oxime (Chart 1, $k_2 > k_{-2}$ and $k_{-1} > k_1$) and the ketone V was recovered as the result of deoximation in liquid sulfur dioxide (Chart 2).

Chart 2.

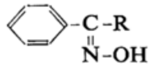


The ultraviolet spectra of the respective specimens and the crude products were recorded in methanol solutions and are seen in Fig. 1—5.

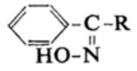
The products were obtained in the pure state or in a comparatively pure state. Sometimes the melting points of the crude products (after being washed with water and dried in vacuo) were in a range such as 135～142°C, but the ultraviolet spectra showed no contamination of another amide and were almost superimposable to the authentic acid amide. It is worthy to note that the formation of the ketone V and the possible contamination of the ketone in small quantity would make the quantitative analysis of the β-oxime impossible by ultraviolet spectrometry, because the ultraviolet spectrum of the ketone V was closely resembling that of the β-oxime. (Fig. 1)

It is a plausible conclusion that the more stable α-oxime I is in the *syn*-phenyl structure VII and the less stable β-oxime II is in the *anti*-phenyl structure VI.

When R (alkyl) is methyl[10], the structure of the oxime is principally of the *anti*-phenyl oxime VI,



VI



VII

because the Beckmann rearrangement affords mainly acetanilide, the phenyl groups migrating. Thus the *anti*-phenyl structure VI of the oxime is favored. As the bulkiness of the alkyl group increases, the presence of the *syn*-phenyl structure becomes more favorable[11].

When R is cyclohexyl, the *anti*-structure VII will be predominant because the steric interference between the hydroxyl group and the puckered cyclohexane ring will be more serious than that between the hydroxyl group and the planer phenyl group. Thus, the α-oxime, structure I, viz. *syn*-phenyl VII, is the more stable form, from which the Beckmann rearrangement should give III by the trans migration.

The rearrangement reaction in liquid sulfur dioxide was so rapid that the isomerization of one isomer to the other or the equilibration between the two oximes could not be competitive against the Beckmann rearrangement reaction, ($k_\alpha \gg k_1$, $k_\beta \gg k_2$, Chart 1). Even the labile β-oxime afforded only the trans migrated product IV on the Beckmann rearrangement. On this occasion the elucidation of Brown et al.[3] may again be recalled to account for the discrepancy of our result.

The complication of the result may be increased if the isomerization and the deoximation of the oxime were accompanied competitively with the rearrangement.

Another point of interest is that when the Beckmann rearrangement was carried out at −70°C in ether as the solvent in place of sulfur dioxide with thionyl chloride as the reagent, α-oxime could not be rearranged, whereas β-oxime rearranged to the acid amide IV smoothly with trans migration. The difference of the reactivity in these solvents and oximes may perhaps depend on the different solvations of the two solvents on oximes and the difference of the reactivity of the two oximes.

That the β-oxime II is more reactive than the α-oxime I is satisfactorily explicable by the facility of producing the intermediate azirinum cation[12] (IIa) by phenyl group participation, and the release of the steric hindrance by rearranging.

In conclusion, the assignment of Meisenheimer and Theilacher[7] has been verified for

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[10] D. E. Pearson and F. Ball, *J. Org. Chem.*, **14**, 118 (1949).

[11] Y. Yukawa, Y. Tsuno and A. Tsukamoto, Abstracts of the 7th Annual Meeting of Chem. Soc. of Japan., April, 1954.

[12] R. Huisgen, J. Witte and I. Ugi, *Chem. Ber.*, **90**, 1844, 1850 (1957).

the geometrical structure of cyclohexyl phenyl ketoximes, the α-oxime being of the *syn*-phenyl and the β being of the *anti*-structure.

Experimental

Material.—The purification and the manipulation of the liquid sulfur dioxide has already been published elsewhere. Thionyl chloride and benzenesulfonyl chloride were used after one distillation respectively1). Bromine was washed with concentrated sulfuric acid and distilled.

Preparation and Separation of Cyclohexyl Phenyl Ketoxime (I) and (II). — Essentially the method of Meyerand Scharvin5) was used and modified slightly. A Grignard reagent from cyclohexyl bromide was reacted with benzaldehyde to obtain the corresponding carbinol, b. p. 130∼135°C (5 mmHg), 26%, which was spontaneously oxidized in the air to cyclohexyl phenyl ketone (V), fine crystals, m. p. 57∼58°C. The oxidation of the ketone resulted in a mixture of the geometrical isomers in good yield. The oximes were dissolved in acetic acid and fractionally precipitated by adding water gradually to obtain first the β-oxime, fine crystals, m. p. 113∼114°C (II), then the α-isomer, fine needles, m. p. 156∼157°C (I), respectively. For compound I. Found: N, 6.64. Calcd. for $C_{13}H_{17}ON$: N, 6.89%. For compound II. Found: N, 6.80. Calcd. for $C_{13}H_{17}ON$: N, 6.89%.

***N*-Cyclohexyl Benzamide(III).**—This material was prepared by the known method8), from cyclohexyl amine and benzoyl chloride in a yield of 82.3%, fine needles, m. p. 148∼149°C (methanol). Found: N, 6.51. Calcd. for $C_{13}H_{17}ON$: N, 6.89%.

Cyclohexanecarboxyanilide (IV).—Aniline and cyclohexanecarboxylic acid was refluxed for several hours and the resulting mass was twice recrystallized from ethanol9), long pillars, m. p. 146.5∼147°C. Found: N, 6.60. Calcd, for $C_{13}H_{17}ON$: N, 6.89%.

Mixed Melting Point of III and IV.—Though the melting points of the two acid amides III and IV, were very close to each other, the mixed melting point of the two materials, III and IV, was depressed to 112∼126°C.

Isomerization of α- or β-Oxime, I or II in Liquid Sulfur Dioxide.—α-Oxime I, (1.0 g.) was dissolved in 300 ml. of liquid sulfur dioxide at −70 ±0.2°C and allowed to stand for 24 hr. No change of melting point of I, 156∼157°C, was seen after the recovery of the material (0.89 g.), which showed no depression of mixed melting point with an authentic specimen. On the contrary, the same treatment on the β-oxime II was carried out at −70°C for 24 hr. and α-oxime was obtained as the result of isomerization which was identified by the mixed melting point measurement with the authentic α-oxime.

The Beckmann Rearrangement.—To a solution of 0.5g. (0.0025 mol.) of the α-oxime in 100 ml. of liquid sulfur dioxide, a reagent (0.0025 mol.), e. g. 0.3 g. of thionyl chloride in a small ampoule was added and the vessel was cooled to a definite temperature in a constant temperature bath. After the mixture reacted to the temperature (−70±0.2°C) the vessel was vigorously shaken in order to break the ampoule in the mixture. The mixture was allowed to stand at this temperature for one hour. Then the mixture was filtered and the filtrate was poured into ice-water. The precipitate afforded was collected, washed with water and dried in vacuo. The product was examined as to its melting point and the mixed melting point with the authentic acid amide, and ultraviolet spectrum of the product was compared in methanolic solution.

As the β-oxime was so unstable in liquid sulfur dioxide that the oxime in a glass ampoule was placed in a mixture of a reagent and sulfur dioxide. The rearrangement by hydrogen chloride or hydrogen bromide was carried out by passing the dry hydrogen halide gas into the reaction mixture at −70°C, followed by the crushing of the ampoule of the oxime.

Ultraviolet Spectra Measurement.—A Hitachi EPU-2A type spectrophotometer was used. All the measurements were carried out in methanolic solution.

Results of the Rearrangements. — *α-Oxime by Thionyl Chloride.*—The melting point of the product (0.42 g.) was 142∼145°C, the mixed melting point with III being 144∼147°C, whereas with IV, the melting point depressed to 112∼116°C. The ultraviolet spectrum was superimposable with that of III. (Fig. 2)

β-Oxime by Thionyl Chloride.—The melting point of the product (0.43 g) was 145∼146°C. No melting point depression with IV, whereas with III it was depressed. The ultraviolet spectrum was superimposable on that of IV. (Fig. 3)

α-Oxime by Benzenesulfonyl Chloride.—The product was recovered α-oxime (0.46 g), melting point and mixed melting point being 155∼157°C.

β-Oxime by Benzenesulfonyl Chloride.—The reaction gave a product (0.44 g.) of meltng point 135∼142°C. The mixed melting point with IV was 136∼145°C. The ultraviolet spectrum was superimposable on that of IV. (Fig. 3) The wide range of the melting point will mean that the reaction was not complete in one hour.

α-Oxime by Bromine.—The result in this case was somewhat complicated, as the Beckmann rearrangement of a phenyl ketoxime by bromine was often accompanied by a bromination of the benzene nucleus13). The ultraviolet spectrum of the crude product was close to that of III, (Fig. 2), however, the melting point of the product (0.43 g.) was 112∼120°C. A fractional crystallization from alcohol yielded two crystals, one melting at 116∼120°C and containing bromine (by the Beilstein test), but was a very small quantity for its further identification. The other was the acid amide III, m. p. 145∼146°C (0.30 g.) and mixed melting point with III was 146∼147°C.

β-Oxime by Bromine.—From the crude product (0.46 g.), the fractional precipitation (from acetic acid solution by adding water), yielded crystals of m. p. 131∼139°C, which was negative for the Beilstein test but was not pure enough. However, the ultraviolet spectrum of this material was resembling well that of IV, (Fig. 3).

α-Oxime by Hydrogen Chloride.—α-Oxime (0.47

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13) N. Tokura, R. Asami and R. Tada, *J. Am. Chem. Soc.*, **79**, 3135 (1957).

g.), melting point and mixed m. p. 154~157°C was recovered. (Fig. 4)

β-Oxime by Hydrogen Chloride.—The ultraviolet spectrum of the product was reproduced in Fig. 5. Two kinds of crystals were separated by fractional precipitation as above mentioned. One, melting point and mixed m. p. 55.56°C (0.40 g.) was the ketone V, 2,4-dinitrophenyl hyrazone, m. p. 198~199.5°C, Found: N, 15.68. Calcd. for $C_{10}H_{20}O_4N_4$: N, 15.21%. The other, (0.12 g.), melting point and mixed m. p. 156~158°C was the α-oxime[1] isomerized from the β-oxime II.

α-Oxime by Hydrogen Bromide.—α-Oxime (0.48 g.), melting point and mixed m. p., 155~157°C was recovered.

β-Oxime by Hydrogen Bromide.—The ketone V, (0.15 g.), meltng point and mixed m. p. 53~55°C, and the α-oxime (0.23 g.), melting point and mixed m. p. 156~158°C, were separated and identified respectively, as above.

α-Oxime by Thionyl Chloride in Ether at −70°C.—The α-oxime (0.33g.) was recovered, melting point and mixed m. p. 155~157°C, (ultraviolet spectrum, Fig. 2).

β-Oxime by Thionyl Chloride in Ether at −70°C.—The product (0.43 g.), melting point and mixed m. p. 142~143.5°C was proved to be the IV. The ultraviolet spectrum was superimposable. (Fig. 3)

Summary

The Beckmann rearrangement of the isomeric cylcohexyl phenyl ketoximes was carried out in liquid sulfur dioxide at low temperature (−70°C) with thionyl chloride, benzenesulfonyl chloride, bromine and hydrogen halides. In liquid sulfur dioxide, the β-oxime was unstable and isomerized slowly to the α-oxime with no reagent. The α-oxime yielded *N*-cyclohexyl benzamide and the β-oxime yielded cyclohexanecarboxyanilide, respectively, by the Beckmann rearrangement in liquid sulfur dioxide. The geometrical structure of the isomers and isomerization between them were discussed. As for the β-oxime, the rate of the rearrangement by far surpassed the rate of the isomerization. The principle of the trans migration in the Beckmann rearrangement has been confirmed within the range of this experiment. The deoximation of the oxime to the parent ketone, cyclohexyl phenyl ketone was observed in the reaction of β-oxime with hydrogen chloride and bromide.

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