g. (0.50 mole) of hydroxylamine hydrochloride in 135 ml. of 75% methanol was stirred at 25° for 2 hr. After removal of methanol under vacuum, the concentrated aqueous mixture was filtered to remove excess hydroxylamine hydrochloride, then extracted with two 100-ml. portions of chloroform. After drying over anhydrous magnesium sulfate, the chloroform solution was concentrated to a residue. The oil was taken up in 200 ml. of ether, from which a small amount of insoluble material separated. The ethereal solution was concentrated to an oil weighing 17.0 g. (68.6 mole %) b.p. 78°/0.25 mm. (dec.); $\lambda_{\max}^{\text{film}}$ 5.54 μ (carbonyl); n.m.r.—3-methyl (triplet) τ 7.84, 4-methylene (quartet) τ 6.58.

Anal. Calcd. for $C_4H_5O_2N$: C, 48.5; H, 5.05; N, 14.1. Found: C, 48.3; H, 5.28; N, 13.8.

3-Methyl-5-phenylisoxazole-4-carboxylic Acid (IIIa).—A mixture of 9.9 g. (0.1 mole) of 3-methyl-5-isoxazolone (VI), 113 g. (0.5 mole) benzoic anhydride and 20 g. of sodium benzoate was stirred at 95–100° for 1 hr. The mixture was cooled, then slurried with 500 ml. of water. The aqueous mixture was filtered to remove insoluble solids, then treated with 200 g. of solid sodium hydroxide. The resulting strongly basic solution was heated at 95–100° for 4 hr., cooled and made acidic (pH 2) with concentrated hydrochloric acid. A crude solid, weighing 12 g., m.p. 110°, separated, which was found to be a mixture of isoxazole acid IIIa and benzoic acid. After two recrystallizations from methanol, there was obtained 3.5 g. (17.2%) of isoxazole acid (IIIa), m.p. 189–190° (lit.,[10] m.p. 189°).

Anal. Calcd. for $C_{11}H_9O_3N$: C, 65.0; 4.47; N, 6.90. Found: C, 65.1; H, 4.41; N, 6.80.

N.m.r. Spectra.—The nuclear magnetic resonance adsorption spectra were determined with a Varian Model A-60 spectrometer. Deuteriochloroform was used as the solvent and the chemical shifts were determined relative to tetramethylsilane as an internal standard. The field was scanned at a rate equivalent to 2 c.p.s. per second over a chart width of 50 cm. The chemical shift was estimated to ±0.5 c.p.s. or a τ value of ±0.01 p.p.m.

Acknowledgment.—We are indebted to Dr. Allen I. Cohen of The Squibb Institute for the determination and interpretation of the n.m.r. data, and to Dr. N. H. Coy and associates for determination and discussions concerning the ultraviolet and infrared absorption spectra. Our appreciation is also extended to Mr. Joseph F. Alicino and his associates for determination of the microanalytical values reported.

Rates of *syn–anti* Isomerization of Phenyl 2-Pyridyl Ketoxime[1]

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A precise method for analyzing mixtures of *syn*- and *anti*-phenyl 2-pyridyl ketoxime for *syn* content was developed using the ability of the *syn* form to form a tris complex with Fe(II). This method is somewhat general and may be used for many other (slow to rearrange) α-amine oximes. The *anti/syn* ratio in the freshly prepared phenyl 2-pyridyl ketoxime is 0.30, which is considerably lower than the equilibrium value showing that the product ratio is determined by the kinetics rather than by the equilibrium constant. In 1 *M* acid or base at 25° the rate of isomerization is slow ($t_{1/2} > 4000$ min.). In the molten state (175°) and in cyclohexanol (161 and 144°) both forms come to equilibrium following a first-order expression ($t_{1/2}$ = 1–30 min.) but k_F/k_R evaluated in this way does not equal K_{eq} suggesting a complex mechanism involving the solvent. The equilibrium *anti/syn* ratio decreased with increasing temperature reflecting the decreased stability of the intramolecular hydrogen bond.

One of the dominant factors in the kinetics of formation of nickel(II) complexes of aliphatic α-amine oximes appears to be the *syn–anti* isomerization rate of the oxime group.[3] In order to evaluate this effect, studies on the kinetic behavior of the *syn–anti* conversion were initiated.

The *syn* and *anti* forms of aliphatic aldo and ketoximes have been shown to exist by Phillips[4a] and by Lustig[4b] using n.m.r. but they have seldom been isolated.[4a,5,6] The rates of isomerism have never been studied but generally the rearrangement is thought to be very fast.

In order to study the rates of isomerism, the pure geometrical forms were needed and an accurate method of analysis had to be developed. The geometrical forms of aromatic oximes had been described and appeared to have rates of rearrangement of a measureable magnitude. Thus an aromatic system was initially investigated as a background for the aliphatic system.

The geometrical forms of an aromatic α-amine oxime, phenyl 2-pyridyl ketoxime, were chosen for study because the *syn*-phenyl form gives a colored Fe(II) complex which may be used for analysis. The lower melting isomer of this oxime was first observed by Tschugaeff[7] and the correct assignment of configuration was made by Huntress and Walker[8]: the lower melting point form (150.5–151.5°) being the *syn*[9] form, the *anti* form melting at 165–167°.

Several studies have shown that concentrated acids and bases, at elevated temperatures, are

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(3) R. Kent Murmann, *J. Am. Chem. Soc.*, **84**, 1349 (1962).

(4) (a) W. D. Phillips, *Ann. N. Y. Acad. Sci.*, **70**, 817 (1958); (b) E. Lustig, *J. Phys. Chem.*, **65**, 491 (1961).

(5) W. R. Dunston and T. S. Dymond, *J. Chem. Soc. Trans.*, **61**, 470 (1892).

(6) P. Hoering, *Ann.*, **332**, 324 (1904).

(7) L. A. Tschugaeff, *Ber.*, **39**, 3382 (1906).

(8) E. H. Huntress and H. C. Walker, *J. Am. Chem. Soc.*, **70**, 3702 (1948).

(9) The designation *syn* refers to *syn*-phenyl and *anti* to *anti*-phenyl.

able to catalyze the *syn–anti* conversion of aromatic oximes[10–12] and there is some evidence that metal ions can also be effective.[13] In general, however, neither the quantitative aspects of the acid–base-catalyzed rearrangement nor the rate expressions are known.

This investigation was undertaken to establish a precise method of analysis for the *syn* form in a mixture using the highly colored iron(II) complex, [Fe(*syn*-phenyl 2-pyridyl ketoxime)$_3$-2H]°, to investigate the magnitude and temperature dependence of the *syn–anti* equilibrium and to determine the kinetic characteristics of the isomerization.

Initial experiments showed that in solution, *syn–anti* rearrangement did not occur at low temperatures. Thus, less than 1% rearrangement occurred on boiling the geometrical forms for one hour in methyl or ethyl alcohol, water, chloroform, or acetone. At a pH of 3 or 9 in water in the presence or absence of Fe(II) less than 1% isomerism takes place in two hours at room temperature. However, boiling with *o*-xylene (144°) or with Fe(II) in water gave appreciable conversion. Catalysis by light was not observed.

The initial unrecrystallized oxime prepared from the purified ketone and hydroxylamine by the method of Huntress[8] gave a value of 77% *syn.* Different preparations varied by less than 3% from this value providing the formation was carried out near room temperature. Samples prepared at high temperatures (90°) gave a smaller proportion of *syn* (60%).

Isomerization in acid and basic solutions was investigated starting with both forms of the ligand. At 32°, after 190 minutes, the following amounts of *syn* were formed from the *anti:* 1 *M* hydrochloric acid (2%), 1 *M* potassium hydroxide (4%), while the amounts of *anti* formed from the *syn* isomer were 3 and 4.2%, respectively. Although the equilibrium concentrations in these media are not known, it is apparent that the rate is slow under these strong acid–base conditions contrary to general opinion. In connection with this it is interesting that in 1 *M* potassium hydroxide, using the average pK_a value of similar oximes (10.8) 99.9% of the oxime is in the ionized form.

TABLE I

RATE OF ISOMERIZATION AT 175°, MOLTEN STATE

Time, min.	% *syn*[a]	% *syn*[b]
0	100.0	0.0
5	60.0	33.5
15	48.0	41.5
25	47.0	44.6
∞	46.9	46.8

[a] Starting with pure *syn*-. [b] Starting with pure *anti*-.

The rate of isomerization in the molten state was also followed with both geometrical forms. Table I gives a sample experiment which shows that equilibrium is reached in about thirty minutes and that both starting materials give the same mixture providing evidence that no decomposition occurs during the reaction time. Assuming the equilibrium is established by simple first-order kinetics, *syn* $\underset{k_R}{\overset{k_F}{\rightleftarrows}}$ *anti*, a graph of ln $(A_0 - A_e / A - A_e)$ *vs.* time should be a straight line and ln $2/t_{1/2}$ should equal $(k_F + k_R)$. When the starting material was pure *syn*, this equation was obeyed with a $t^1/_2$ of 2.5 ± 0.1 min. However, isomerism of the *anti* form showed first-order behavior for only the initial two half-lives and was followed by a slightly slower rate. $(k_F + k_R)$ evaluated from the first two half-times was the same as that obtained with the *syn* form. K_{eq} had a value of 1.13 ± 0.02 at 175°. Using this value and a half time for *syn* or *anti* conversion of 2.5 min., gave k_F = 0.15 min.$^{-1}$ and k_R = 0.13 min.$^{-1}$. The slight deviations from first-order behavior when using the *anti* form are not understood but may be due to trace impurities in the original amineoxime reactant or to a somewhat larger experimental error in measuring such a rapid rate.

With cyclohexanol as the solvent at 161°, slower rates were obtained but they were complicated by slow simultaneous decomposition. This amounted to 4% over a period of six hours. Since the half-time of reaction was about twenty minutes, this side reaction could be corrected for in the estimation of K_{eq} but because the kinetics of the decomposition was not known an estimation of the rate constants was not made. At 161°, in cyclohexanol the per cent *syn* at equilibrium is 39.0 corresponding to K_{eq} = 1.56 ± 0.03.

At 144°, in cyclohexanol less than 1% decomposition was observed in 300 minutes. Figure 2 gives sample results for both isomers. At equilibrium 36.1% *syn* was found corresponding to K_{eq} = 1.78 ± 0.02. Within experimental error both rates were first order in amine oxime but the half-times differed greatly; *syn* $t_{1/2}$ = 34 min., *anti* $t_{1/2}$ = 67 min., showing that isomerism in this solvent must proceed by a complex mechanism.

The addition of trace amounts (10^{-5} moles/l.) of Fe(II), Ni(II), or Cu(II) caused an increase in the rate of conversion of *anti* to *syn.* The rate increases by a factor of about 100 over the noncatalyzed rate but precise interpretation of the spectral results is somewhat uncertain due to the colored complex of the respective metal being formed simultaneously with the *syn* form.

The values for K_{eq} increase with increasing temperature, (the *anti*-phenyl form being favored at low temperatures) whether in the molten state or

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[10] A. W. Stewart, "Stereo Chemistry," 2nd ed., Longmans Green & Co., New York, N. Y., 1919, pp. 131–145.

[11] G. Wittig, "Stereochemie," Akademische Verlagsgesellschaft, Leipzig, 1930, pp. 182–200.

[12] J. Meisenheimer and W. Theilacker, *Ann.*, **469**, 218 (1929).

[13] A. Bryson and F. P. Dwyer, *J. Proc. Roy. Soc. N. S. Wales*, **74**, 107 (1940); J. Meisenheimer and W. Theilacker, "Stereochemie," K. Freudenberg, ed., Vol. 3, Edwards Brothers, Ann Arbor, Mich. 1945.

dissolved in cyclohexanol. A comparison of log K_{eq} *vs.* $1/T$ shows that intermolecular associations are also important because the values in cyclohexanol cannot be quantitatively compared with those in the molten state. The qualitative effect of temperature on K_{eq} suggests a change over from intra- (with the pyridine nitrogen), to intermolecular (with solvent molecules), hydrogen bonding with increasing temperature.

Experimental

Materials.—The mixture of *syn*- and *anti*-phenyl 2-pyridyl ketoxime was prepared from phenyl 2-pyridyl ketone by the method of Diehl and Smith[14] and the isomer separation carried out by the method of Huntress and Walker.[8] The *anti* form prepared in this manner was free of the *syn* form and gave no color with Fe(II).

A method developed later gave improved yields of purer *anti*. The crude amineoxime containing about 23% *anti* was converted to the equilibrium mixture (53.1% *anti*) by warming it to 175 ± 5° for 35 min. After cooling, it was dissolved in a small quantity of methanol and slightly over the calculated amount of $[Ni(H_2O)_6]Cl_2$ was added (based on its reaction with the *syn* form in a 2:1 metal/ligand ratio). After 10 min. the volume was increased by a factor of five with cold water in which the Ni(II) complex is soluble and the product collected by filtration at 0°. Two crystallizations from methanol–water mixture gave a white product melting at 166–167°[8]; yield 85%.

Anal. Calcd. for $C_{12}H_{10}N_2O$: C, 72.70; H, 5.02; N, 14.14. Found: C, 72.4; H, 5.09; N, 14.21.

The *syn* form was prepared by recrystallization of the crude oxime (77% *syn*) from chloroform and methanol and had a melting point of 150.5–151.5°. Contamination of the *syn* form by the *anti* is less than 0.3% on the basis of mixed melting points, infrared spectra, and agreement (2/600) in the colorimetric *syn* determination of two samples prepared under radically different conditions.

The distilled water and solvents used were free from iron as determined by the use of the ligand as a colorimetric reagent and all other chemicals were reagent grade and tested for Fe(II).

Spectrophotometric measurements were carried out with a Beckman DU spectrophotometer using 1-cm. matched silica cells in a constant temperature compartment controlled to ±0.01° with a stream of water passing through cell-spacers.

Analytical determination of the *syn* form was carried out using the color of $[Fe(syn\text{-phenyl-2-pyridyl ketoxime})_3\text{-}2H]^0$ formed with Fe(II). The *anti* form does not react and the catalytic conversion (*anti*→*syn*) is very slow under the conditions employed. The complex formation is slow and under the conditions employed incomplete which requires that the time between the addition of reagents and the absorption measurement be constant. The absorption at 545 mμ is characteristic of this complex, and neither the molar absorbancy nor the wave length of maximum absorption is changed by moderate (0.1 *M*) concentrations of colorless salts, amines, ketones, or alcohols. The absorption is, however, sensitive to pH, Fe(II)/ligand ratio, temperature, and time of reaction requiring careful reproduction of conditions to give reproducibility of better than 1%.

To 20 ml. of buffer (1 *M* NaAc and 1 *M* HAc) was added 10 ml. of a 1/3 v./v. acetone–water solution containing 6.00 mg. of the mixed amineoxime. To this was added 10 ml. of a 3.33×10^{-3} *M* $(NH_4)_2Fe(SO_4)_2 \cdot 6H_2O$ solution containing 4 ml./l. of concentrated sulfuric acid. Then 70.0 ml. of acetone was added (to solubilize the complex) and the volume made up to 200 ml. using water. The above operations were carried out as rapidly as possible and *exactly* 60 min. at room temperature was allowed for the complex formation before measurement of the optical density at 545 mμ. The temperature during the complex formation is not important for a change of 25° makes only a 1% change in the final absorbance.

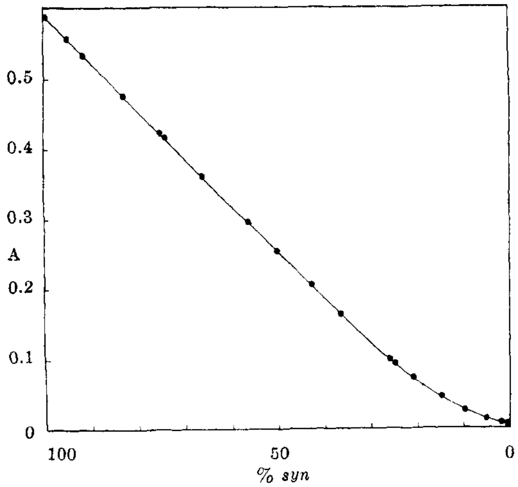

Fig. 1.—The relation of absorbance to % *syn* in synthetic mixtures. *syn* + *anti* = 6.00 mg./200 ml., 545 mμ, 1.66×10^{-4} moles/l. Fe(II), buffered with 1–1 sodium acetate–acetic acid (0.10 moles/l.) in 35% v./v. acetone–water. 1.00-cm. cell.

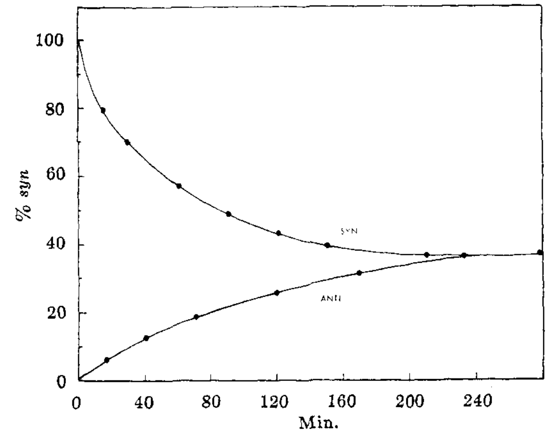

Fig. 2.—Rate of isomerization of *syn* and *anti*; 144°, in cyclohexanol.

The analysis of synthetic mixtures of *syn*- and *anti*-phenyl 2-pyridyl ketoxime was carried out using a final concentration of total oxime of 0.02 mg./ml. The smallest amount of *syn* detectable was slightly less than 0.0002 mg./ml. in a 1.00-cm. cell. Figure 1 shows the relationship between the absorbance and the per cent *syn* in a synthetic sample. In the lower region the excess of Fe(II) becomes very large and thus lower complexes are favored causing large deviations from linearity.

Using synthetic mixtures as standards and Fig. 1, it was shown that the amount of *syn*-phenyl 2-pyridyl ketoxime in a 6-mg. sample could be determined with a precision of ±0.2%.

Isomerization–Fused State.—The carefully dried isomer (6.00 mg.) was placed in a pre-heated test tube submerged in a constant temperature bath at 175 ± 1°. At 175° no volatilization occurred and decomposition or oxidation was less than 1% in 1 hr. Melting took place rapidly and after

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[14] H. Diehl and G. F. Smith, "The Iron Reagents, Bathophenanthroline, 2,4,5-Tripyridyl-2-triazine and Phenyl 2-Pyridyl Ketoxime," G. F. Smith Co., Columbus, Ohio, 1960, pp. 43–50.

the required time the reaction was quenched by immersion in cold water. Analysis for *syn* content was then carried out in the fashion described.

Isomerization in Solution.—A 50.00-ml. sample of cyclohexanol was heated in the top compartment of a constant temperature apparatus maintained (±1°) at the desired temperature by boiling cyclohexanol (161°) or *o*-xylene (144°) in the lower compartment. When constant temperature was attained, 60.0 mg. of the desired isomer of pure amine oxime was added. At measured intervals, 5-ml. samples were withdrawn, quenched in cold water, and analyzed for *syn* content. The presence of cyclohexanol did not interfere with the spectral analysis.

In basic or acidic regions in water, samples containing 6.00 mg. of the amine oxime were removed at measured intervals, neutralized with either acid or base to a pH of 7 using a Beckman Model GS pH meter and analyzed for *syn* content.

Three-membered Rings. V. The Formation of Cyclopropanes Substituted at All Three Ring Carbons. A Steric Analysis

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The reaction of some α,β-unsaturated esters and α-chloro esters in the presence of sodium hydride to form cyclopropanes substituted on all three of the ring carbons has been examined. The yields of diesters and the isomer ratios for each set of reactants has been determined in both polar and nonpolar media. Solvent effects, although present, are masked to a large extent by other effects, mainly steric in origin. The combination of effects in most cases leads to mixtures of isomers, but with certain patterns of substitution a fairly high degree of stereoselectivity may be observed in the nonpolar solvents. One β-substituent in the α,β-unsaturated ester produces no appreciable effect on the yield of the substituted cyclopropane, but an α,β-disubstituted acrylic ester results in decreased yields, and a β,β-disubstituted ester does not result in any isolable product.

In previous papers of this series the formation of cyclopropanes substituted on only two of the ring carbons has been examined.[2a,b] A major reason for this choice was that the products could exist in only two stereoisomeric forms, one *cis* isomer and one *trans* isomer. The present report concerns the extension of these studies to some examples of the more general case in which all three carbon atoms of the cyclopropane nucleus are substituted. We have limited our examples to esters, but on the basis of the earlier work we expect that the conclusions presented here can be extended to similar compounds in which ester groups are replaced by nitrile or related functional groups.[2a,b]

These more general cases are more complex than those previously studied for three reasons: (1) As many as four stereoisomeric products may be formed; (2) The intermediate anion may exist in two diastereomeric forms; and (3) The starting olefinic component may exist in either *cis* or *trans* form. These points are illustrated by the following equations which also summarize the compounds studied in this work.

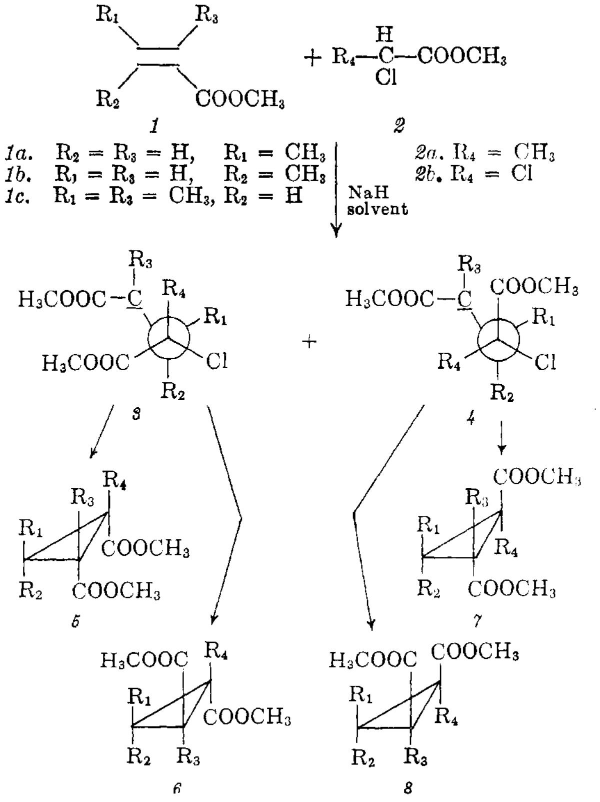

Chart I

Results

Yields of Ester Mixtures.—The products, mixtures of stereoisomeric esters, are generally obtained in satisfactory yield from monosubstituted acrylic esters, the substituent being in either the α-[2a,b] or β-position. With a disubstituted acrylic ester the yield of product drops markedly. This decrease is almost certainly due to hindrance in the initial Michael addition (Chart I). For reactions with α,β- or β,β-dimethyl acrylates much starting material was recovered. If this recovered ester is taken into account in the α,β-

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[2] (a) L. L. McCoy, *J. Org. Chem.*, **25**, 2078 (1960); (b) L. L. McCoy, *J. Am. Chem. Soc.*, **84**, 2246 (1962).