[FROM THE DEPARTMENT OF CHEMISTRY, VANDERBILT UNIVERSITY]

# THE BECKMANN REARRANGEMENT. THE REARRANGEMENT OF SOME SUBSTITUTED ACETOPHENONE OXIMES IN SULFURIC ACID

## D. E. PEARSON AND FRANCES BALL

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## GENERALIZATIONS

The Beckmann rearrangement has been justifiably called the "Mona Lisa" Meisenheimer, Kuhara, and Chapman have made outstandof rearrangements. ing contributions to the understanding of the reaction, while Blatt (1) and Jones (2) have adequately summarized the countless experiments of these and other workers. Nevertheless, some of the generalizations that have grown from their studies and become accepted almost as axioms to explain all phenomena of the Beckmann rearrangement, were originally based on specialized and sometimes limited reactions which may not apply generally. Chapman's work, for instance, was based on the rates of rearrangement of oxime picryl ethers in polar organic solvents (3, 4), which is a quite different environment than sulfuric acid or phosphorus pentachloride in ether, the usual rearrangement media. It is the purpose of this paper and subsequent ones to apply the concepts of Chapman et al. to more practical conditions, and to confirm or modify their conclusions. To do so, it is helpful to develop and to summarize in outline form the generalizations concerning mechanism and configuration which have fewest exceptions:

1. Step 1. A salt-like complex is first formed between the oxime and the rearrangement agent, usually an exothermic reaction. So much heat is occasionally evolved that it is sometimes mistaken by investigators for the rearrangement proper. It can be demonstrated in most cases that the step is reversible by aqueous decomposition of the complex to the original oxime.

2. Step 2. An ester (or picryl ether) grouping of a type that is potentially capable of ionization is next formed from the complex by elimination of water or of some other simple molecule. The majority of cases, particularly with phosphorus pentachloride as an agent, comply with this generalization, though exceptions can be found. For example, Lachmann's rearrangement of benzophenoxime in aqueous hydrochloric acid (5) is difficult to imagine as proceeding through an ester formation step. Yet, Chapman (6) presents evidence that an ester-like compound may form under these circumstances from the reaction of the oxime and N-phenylbenzimidyl chloride, the latter arising from the action of hydrochloric acid on benzanilide. It is at least noteworthy that all effective agents for the rearrangement are electrophilic in nature and capable of forming esters with the oxime.

It is emphasized that the following generalizations refer to a single step (3A) and are made separable only for the sake of describing the dual nature of the forces within the molecule which affect rearrangement.

3. Step 3A. The ease of ionization of the ester partly determines the rate and/or

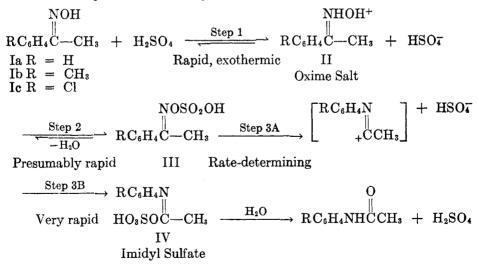
ease of rearrangement.<sup>1</sup> As one of many illustrations, Kuhara (1) has shown that the acetate esters of oximes rearrange more slowly than chloroacetate esters which, in turn, rearrange more slowly than benzenesulfonic esters. Also, it is well known that the rearrangement rate is increased by choice of a solvent of high dielectric constant, which would favor ionization.

4. Step 3A. The rate and/or ease of rearrangement partly depends on the relative tendency of the migrating group to donate a pair of electrons to the nitrogen atom by migration of the entire group (3, 4, 9). Generalizations 3 and 4 are, therefore, visualized as a "push and pull" process entirely analogous to Bartlett's theory as applied to the pinacol rearrangement (7). The ionization of the ester is considered to be the "pull" and the migration tendency of the migrating group to be the "push". Chapman (3, 4) has further shown that the nonmigrating group has the same relative tendency to influence migration rates but to a much lesser extent. The above generalizations permit no explanation of the latter phenomenon. A possible explanation is made later at a more appropriate place in the discussion. Generalization 4 is confirmed by the following supplementary statements:

a. The migrating group which attaches itself to the nitrogen atom is anti to the hydroxyl group in the original oxime. Though anti attachment of groups was surprising to early workers, it is now considered to be a normal attachment from consideration of the mechanism of many other reactions. Certainly, it is an essential feature of Bartlett's "push and pull" theory (7).

b. The migration of the alkyl or aryl group takes place intramolecularly. This is another confirmation of the inseparable nature of generalizations 3 and 4, and its truth has been amply demonstrated by Campbell and Kenyon (8).

The generalizations are illustrated by the following equations using the oximes and conditions pertinent to the experimental work:



<sup>1</sup> The rate comparison is obvious, and the ease of rearrangement is correlated arbitrarily with the heat of activation. The ion is bracketed in Step 3A to show its momentary, fleeting existence. However, the imidyl sulfate existence is definitely real, as Coleman and Pyle (10) have utilized similar products of the Beckmann rearrangement in the preparation of other compounds.

## DEVELOPMENT OF METHODS OF ANALYSIS FOR RATE STUDIES

To study the above reactions it was essential to develop a method of analysis for accurate determination of either the oxime or the amide in the presence of one another and in the presence of sulfuric acid. Sluiter (11) had previously measured the rate of rearrangement of acetophenoxime by determining the amount of acetic acid from the hydrolyzed amide. But, in the hands of the Vanderbilt investigators, it yielded erratic results even with obvious improvements; the average yield was  $95\% \pm 4\%$  for 22 samples. The 2,4-dinitrophenylhydrazine analysis of Iddles (12) was next tried and proved to be satisfactory for the determination of acetophenoxime (99.2%  $\pm$  2%) and less so for the *p*-chloro derivative  $(98\% \pm 2.5\%)$  and the *p*-methyl derivative  $(95\% \pm 4\%)$ . The higher the melting point of the hydrazone the more accurate were the results. Details of the method are given in the experimental. After accumulating considerable data in this manner, the method was finally abandoned for one of more accuracy, greater ease of manipulation and of wider scope. It consisted of oxidizing the oxime with ferric sulfate and titrating the ferrous sulfate with potassium dichromate, a procedure adapted from the paper of Bray, Simpson, and MacKenzie (13). Even with this method, difficulties were encountered, as aromatic amides (but not aliphatic amides) underwent slight but noticeable oxidation by ferric sulfate. Correction curves were, therefore, necessary. The accuracy can best be judged by the "pseudo runs" shown in the experimental.

## PRESENTATION OF RESULTS

The rearrangements followed first order rate curves corroborating results of Sluiter. Sluiter's work, in addition, has shown that the first-order rate constant in excess sulfuric acid remained unchanged over an appreciable range of oxime concentration. Accordingly, all runs in this paper were made *approximately* at one concentration. The experimental results of the oxidation method are presented in Table I and compared with the results of the dinitrophenylhydrazone method and Sluiter's data in Table II.

A comparison of Table I and Table II shows that the results do not agree well enough to draw absolute conclusions about the rate constants, activation energies or entropies. Table I is perhaps nearest the truth, but both tables are considered relatively accurate enough for qualitative conclusions to be drawn. In Figure 1, the logs of the rate constants are plotted against reciprocal temperatures to illustrate the validity of application of the Arrhenius equation to the rearrangement reaction.

### DISCUSSION OF RESULTS

It is evident from Table I that Chapman's results have been substantiated as given in Generalization 4. The rates of rearrangements were found to be in the

## TABLE I

RATE CHARACTERISTICS OF THE REARRANGEMENT OF ACETOPHENONE OXIMES IN SULFURIC ACID (OXIDATION METHOD)<sup>a</sup>

OXIME NOH RCaH4CCH1	т°С	k <sup>b</sup>	HALF-LIFE <sup>c</sup>	EAd	Δ\$*
$\mathbf{R} = \mathbf{H}$	50.9 60.9 64.9	0.0011 .0036 .0053	630 190 130	24	-8
$R = CH_3$	40.9 50.9 55.9	.0004 (3) .0021 .0039	1600 330 180	24.5	-5
$\mathbf{R} = \mathbf{Cl}$	50.9 55.9 60.9	.0007 .0012 .0022	990 580 310	22.5	-14

 $^{\circ}$  All rates run with approximately 0.0226 mole of oxime in 25 cc. of 95.5% H<sub>2</sub>SO<sub>4</sub>.

<sup>b</sup> k = 
$$\frac{2.303}{t} \times \log \frac{a}{a-x}$$
; reciprocal minutes.  
<sup>c</sup> t<sub>i</sub> =  $\frac{0.693}{k}$ ; minutes.  
<sup>d</sup> log  $k_2/k_1 = \frac{E_A}{2.303R} \times \frac{T_2 - T_1}{T_2T_1}$ ; kilocalories.  
<sup>e</sup> k =  $\frac{KT}{h} (e^{\Delta S/R}) (e^{-E_A/RT})$ ; entropy units.

# TABLE II

RATE CHARACTERISTICS DATA FROM SLUITER AND FROM 2,4-DINITROPHENYLHYDRAZONE METHOD

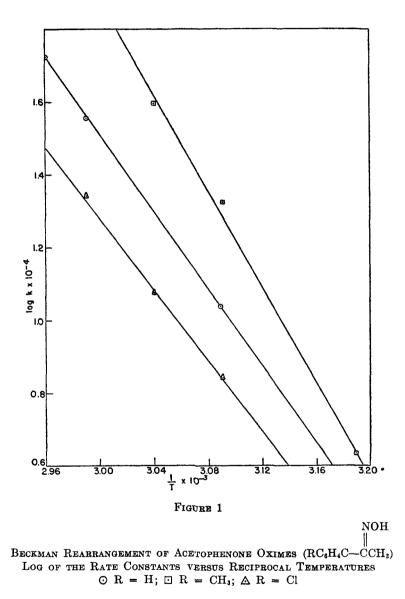
CXIME	conc. of H2SO4	т°С	k	HALF-LIFE (MINUTES)	EA	METHOD
R = H	93.5	61	0.0023	300		DNPH <sup>a</sup>
	96.0	61	.0027	250		
	96.0	71	.0083	85	25.5	
	100.0	61	.0040	170		
$R = H^b$	93.6	65	.0019	160		Sluiter
¢	93.6	65	.0019	160		
¢	93.6	60	.0011	275	$24.5^{d}$	
c	97.2	60	.004	75		
$R = CH_3$	96.0	51	.0019	360		DNPH
	96.0	61	.0065	110	26.5	
$\mathbf{R} = \mathbf{Cl}$	96.0	61	.0020	350		
	96.0	<b>7</b> 1	.0060	110	25.5	
R = H	96.0	61	.0042	170		
Oxime Acetate	96.0	71	.0136	50	26.5	

<sup>a</sup> DNPH-Dinitrophenylhydrazone method. Concentration same as Table I, unless designated as b or c.

<sup>b</sup> Conc.: 2.5 g. Oxime/100 cc. H<sub>2</sub>SO<sub>4</sub>. <sup>c</sup> Conc.: 2.5 g. Oxime/50 cc. H<sub>2</sub>SO<sub>4</sub>.

<sup>d</sup> Calc'd in this laboratory.

order: p-methyl derivative (Ib) > acetophenoxime (Ia) > p-chloro derivative (Ic). In a practical sense, therefore, the results have been quite satisfactory. A general idea of the conditions and times for complete rearrangement can be obtained by reference to the tables. Also, if electronic interpretations continue



to hold, some qualitative predictions may be made as to other oxime rearrangement rates. Aliphatic oximes should rearrange more slowly than aromaticaliphatic oximes, and aromatic oximes should rearrange slightly faster than the aromatic-aliphatic oximes. If electronegative groups are attached to the migrating or non-migrating group, the rates should be slower or slightly slower respectively. Exceptions will possibly be found in later work as the entropy terms ( $\Delta$ S) are not constant. In fact, the rearrangement is so intricate, considering complex formation, reagent characteristics, and consequences of consecutive reactions, that it is perhaps fortunate that the rate sequence was in the order predicted from the generalizations. With acetophenoxime, the situation was further complicated by sulfonation, contrary to textbook statements (14). Such complications were reflected in the activation energies and entropy terms, which could not be resolved into simple, qualitative relationships. For that matter, Chapman's activation energies and entropy terms (the latter calculated in this laboratory) were as difficult to analyze.

An interesting aspect of Table II results is the great dependence of the rates of reaction on sulfuric acid concentration. Hammett and Deyrup (15) explain this phenomenon as due to the "hyperacidity" of the sulfuric acid and show that the rates parallel the acidity function,  $H_0$  (16). Their explanation would hold as well' if it is considered that the esterification rate (Step 2) is dependent on the sulfuric acid concentration. This would mean that sulfate formation (Step 2) was the rate determining step of the rearrangement and that all above predictions on rates of rearrangement in sulfuric acid applied to the esterification reaction. The slightly greater activation energy of acetophenoxime acetate as compared to the oxime itself (comparison by Table II only) might be interpreted in this light as a slight blocking of sulfate formation by the acetate radical. The assumption was at least worthy of consideration, and efforts were made in the next part of this paper to isolate the acetophenoxime-O-sulfonic acids (IIIa, b, and c), possible intermediates in the rearrangements of the oxime in sulfuric acid, and to investigate their behavior.

## ISOLATION AND CHARACTERISTICS OF THE ACETOPHENOXIME-O-SULFONIC ACIDS

Sanford, Sherk, et al. (17) have described the formation of acetanilide from the exothermic reaction of acetophenone and hydroxylamine-O-sulfonic acid but stated that the sulfonic ester was probably not an intermediate. Smith (18) described the preparation of the potassium salt of acetophenoxime-O-sulfonic acid and its rearrangement to acetanilide by 4 N HCl in dioxane. It thus appeared possible to isolate acetophenoxime-O-sulfonic acid and its p-substituted After numerous trials, it was found that the simple addition of the derivatives. oxime to chlorosulfonic acid in ether solution precipitated the desired acid. The study of these acids, (IIIa, b, and c), however, was another matter, as they were hygroscopic, unstable, and easily hydrolyzed to the oxime salts (IIa, b, and c). A more complete description is given of the most tractable acid, the *p*-methylacetophenoxime-O-sulfonic acid. It was a white, free-flowing powder (acid equiv. calc'd: 229; found: 219.5) which decomposed abruptly when heated on a spatula, when touched with a hot wire, or when immersed in a bath at 80° (flashes at 84° and resolidifies). When suspended in ethylene chloride, it was converted exothermically at about 45° into at least 80% p-methylacetanilide. If placed in a loosely stoppered weighing bottle, it was slowly hydrolyzed to the oxime salt (IIb) (acid equiv. calc'd: 123.5; found: 127.5), which did not rearrange

in refluxing ethylene chloride; rather, a 91% yield of oxime was obtained. The other oxime acids behaved similarly. The *p*-chloro derivative (IIIc) gave a better acid equivalent but was more hygroscopic. The acetophenoxime-O-sulfonic acid (IIIa) was so reactive that the removal of the last trace of solvent at room temperature brought about spontaneous decomposition, unless special precautions were taken.

The above description implies that the acetophenoxime-O-sulfonic acids are so reactive that they undoubtedly rearrange spontaneously in sulfuric acid at the temperature of rearrangement *provided they are intermediates*. The ratedetermining step would, therefore, be the oxime-O-sulfonic acid formation (Step 2) an assumption which would alter general concepts of the rearrangement. It would mean that the correlation of group tendency to migrate (considered as a part of the rate-determining step) has been communicated to the oxime hydroxyl group by controlling the rate of esterification——perhaps as simple a matter as an increase or decrease of acidity of the oxime hydroxyl group. The influence of the *non-migrating* aryl or alkyl group on reaction rates would thus be explained, since it, too, would affect the acidity of the oxime.

However, the actual behavior of the acetophenoxime-O-sulfonic acids in sulfuric acid cast some doubt on belief that they were intermediates. At low temperature, they were converted to the oxime salt (II), illustrating the reversibility of Step 1, and at high temperature they underwent almost an explosive decomposition, giving serious side-reactions. At intermediate temperatures, they were partly converted to amides in yields greater than estimated from the reaction rate constant. However, this may have been due to local heating effects, as considerable heat was evolved in introducing the oxime esters into sulfuric acid. The question will best be decided by other experimental means with more workable intermediates.

Whether the oxime-O-sulfonic acids are intermediates or not, the spontaneity of their rearrangement suggests that either ester formation (Step 2) is the ratedetermining step, or one of lower activation energy level than ester formation. The only likely possibility is the elimination of water from the oxime salt, as postulated by Lachmann (5):

$$\begin{array}{ccc} & & & \\ &$$

The latter step still indicates that the rearrangement tendencies of oximes in sulfuric acid are determined by an earlier step than the actual rearrangement (Step 3A). In other words, the actual migration of the aryl group or alkyl group of the oxime in sulfuric acid appears to be an extremely rapid and exothermic reaction. It is, therefore, interesting to note that Chapman's work, involving the rearrangement of picryl ethers of the oximes in polar organic solvents, and the work of this paper, involving sulfuric acid rearrangement, have different rate-determining steps and yet yield qualitatively the same rate sequences and the same approximate energy requirements. It could be best explained, in the opinion of the authors, on the basis of the parallelism of migration tendencies and of other chemical functions of the oximes.

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### EXPERIMENTAL

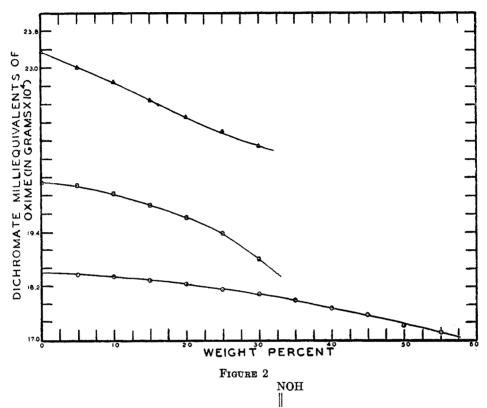
#### Part I. Reaction Rate Measurements

A. Oxime purifications. The oximes were prepared by standard methods, recrystallized at least once from methyl alcohol and finally from cyclohexane. Acetophenoxime (Ia), m.p. 57.5-57.8°; acetophenoxime acetate, m.p. 55-56°, mixed m.p. with I: below room temperature; p-chloro oxime (Ic), m.p. 97.5-98°; p-methyl oxime (Ib) m.p. 87-88°. All of the oximes were stored in evacuated desiccators over soda lime.

B. Development of oxime determinations. 1. The acetic acid method. Sluiter's procedure (11) was rejected on first trial as the distillate gave positive sulfate tests. The following modifications helped: a series of accurately weighed acetanilide samples from 0.05 g. to 0.2 g. was dissolved separately in 20 cc. of water and 1 cc. of concentrated sulfuric acid contained in a 50 cc. distilling flask with condenser. The sulfuric acid was neutralized with 0.5 N alkali to methyl orange end-point and made slightly acid again with dilute sulfuric acid. In this manner the sulfuric acid was converted to sodium acid sulfate. The solution was distilled until no more vapor could be forced over. Since bumping was a serious problem, the distillate was redistilled. The condensers were washed after each distillation and added to the distillate. The distillate was then titrated with 0.1 N sodium hydroxide to phenolphthalein end-point. Twenty-two samples gave yields of 95% acetic acid  $\pm 4\%$ . No further work was done by this method.

2. The 2,4-dinitrophenylhydrazine method (12). Samples of oxime, varying in weight from 0.05 g. to 0.2 g. were individually suspended in 15 cc. of water, and one cubic centimeter of concentrated sulfuric acid and an amount of 2,4-dinitrophenylhydrazine equivalent to 100% excess were added to the suspension. The initial samples, containing large amounts of oxime, usually required about 0.3 g. of hydrazine and, as the oxime concentration became smaller, about 0.1 g. A constant amount of 2,4-dinitrophenylhydrazine made no difference in the gravimetric procedures, but the washings of the precipitate were more difficult with the smaller samples of oxime. The hydrazone formed a yellow, flocculent precipitate immediately, but the mixture was heated on a steam-bath to ensure complete reaction. The samples were then cooled and diluted to approximately 450 cc. The hydrazone, either before or after dilution could not be allowed to stand overnight as the excess 2,4-dinitrophenylhydrazine in dilute sulfuric acid formed a bright, red compound which could not be washed out. The dilution was essential as the hydrazone was somewhat soluble in more concentrated solutions of acid. Furthermore, the filtrations were easier after dilution due to the character of the precipitate. The precipitate was then filtered through Gooch crucibles with asbestos, washed with 125 cc. of 2 N HCl and with about 400 cc. of hot water until the filtrate was colorless. The crucibles were dried at 100-105° overnight or to constant weight. Acetophenone-2,4-dinitrophenylhydrazone yields:  $99.2\% \pm 2\%$ , 15 samples; *p*-chloro derivative  $98\% \pm 2.5\%$ , 8 samples; *p*-methyl derivative  $98\% \pm 3\%$  at 0.1 g. oxime concentration and  $92.5\% \pm 3\%$  at 0.05 g. oxime concentration, 20 samples. The analysis of the p-methyl derivative was improved somewhat by adding 2 cc. of concentrated ammonium hydroxide before addition of 2,4-dinitrophenylhydrazine.

3. The oxidation method (13). The analyses were made comparable to actual runs. Accurately weighed mixtures of the oximes and the rearrangement product (usually the amide but, in the case of acetophenoxime, sulfanilic acid) were suspended in 25 cc. of water contained in a 150-ml. beaker covered with a watch glass. After the addition of 1 cc. of concentrated sulfuric acid, the suspension was heated and held near the boiling point for 5-10 min. or until the crystalline oxime became oily. The samples were then removed from the hot plate, the sides of the beaker and the watch glass washed with a stream of distilled water and 0.8 g. of ferric sulfate added. Again the samples were heated and boiled gently for 5 min. After removing from the hot plate, the sides of the beaker were again washed and 5 cc. of benzene added to prevent oxidation of the ferrous sulfate while cooling in an ice-bath. Phosphoric acid (50%, 10 cc.) and 6 drops of sodium diphenylaminesulfonate



Determination of Acetophenone Oximes ( $RC_6H_4C$ — $CH_3$ ) in Presence of rearranged Product (Oxidation Method)

Dichromate milliequivalent of oxime versus weight per cent of rearranged product<sup>a</sup>.

- $\odot$  R = H and Sulfanilic Acid
- $\square R = CH_3$  and p-Methylacetanilide
- $\triangle \mathbf{R} = \mathbf{Cl}$  and p-Chloroacetanilide

<sup>a</sup> Points are composites of at least 4 determinations for each point.

solution (19) were added, and the samples immediately titrated with 0.027 N potassium dichromate. Approach of the end point is indicated by the appearance of a bright green color which is changed by the addition of one more drop to a purple color. The presence of the rearrangement product had a noticeable but reproducible effect on the milliequivalence of the dichromate as indicated in Figure 2.

Since the correction factor was appreciable above 40% rearranged product, no runs were sampled beyond this limit. In calculating unknown oxime concentrations, a method of approximation was used as follows: the original weight of oxime with zero per cent rearranged product was known and required Y cc. of dichromate. The unknown sample required X cc. to titrate. Therefore, X/Y gave the per cent rearranged product from which the approximate milliequivalence of the dichromate solution could be selected from the curve (Fig. 2). After calculation of the concentration of the oxime, this figure, a more accurate one, was used to calculate X/Y again, from which the correct milliequivalence of the dichromate solution could be selected. Pseudo runs were made to check the accuracy of the method whereby mixtures of oxime and rearranged product were weighed out by the senior author and titrated by the junior author. The results are given in Table III.

NOH    RC4H4CCH1	WEIGHT PERCENT REARPANGED PRODUCT	WEIGHT OF OXIME	WEIGHT OF OXIME CALC'D
R = H	Sulfanilic Acid		
	0	0.0752 g.	0.0750 g.
	8.35	.0700	.0696
	16.4	.0652	.0658
	24.2	.0602	.0602
	31.8	.0550	.0551
	39.2	.0503	.0501
$\mathbf{R} = \mathbf{CH}_{3}$	<i>p</i> -Methylacetanilide		
	3.3	0.0725	0.0730
	6.8	.0699	.0687
	10.0	.0675	.0667
	13.5	.0649	.0653
	20.0	.0600	.0590
	26.2	.0554	.0563
$\mathbf{R} = \mathbf{Cl}$	p-Chloroacetanilide 0		
	11.4	0.0797	0.0805
	20.0	.0751	.0760
	25.0	.0675	.0706
	30.2	.0628	.0647
	25.0	.0674	.0698
	22.0	.0703	.0690

#### TABLE III

PSEUDO RUNS FOR DETERMINATION OF OXIME CONCENTRATIONS IN PRESENCE OF REARRANGED PRODUCTS (OXIDATION METHOD)

C. Rate determinations. Approximately 0.0226 mole of oxime was weighed accurately and placed in a test-tube, 17 x 2.5 cm., with a ground-glass stopper. Sulfuric acid (25 cc., Merck, C.P.) was pipetted into a tared, dry flask, weighed, then poured into the test-tube which contained the oxime. The flask was reweighed to obtain the weight of sulfuric acid to 0.01 g. With acetophenoxime and the p-methyl derivative, it was necessary to cool the test-tube. When the oxime had dissolved, the test-tube was immersed immediately in a constant temperature bath and the temperature was maintained at  $\pm 0.02^{\circ}$ . At various intervals aliquots were removed with a 1-cc. pipette and the amount of sulfuric acid delivered determined by weighing the pipette before and after delivery of the sulfuric acid solution to a 150-cc. beaker containing 25 cc. of water. The aliquots were then treated exactly as shown in B-3. The weight of oxime found was then converted by the aliquot factor to weight of oxime left in original sample, which figures are given in Table IV.

NOH II RC4H4C—CH3 T°C	part Aoxidation method									
	0	0.5	1.0	1.5	2	3	4	6	8	10
R = H										
50.9	64.5		60.4		56.9		49.8	43.2	38.5	35.5
	64.7		61.2		56.5		50.3	43.0	39.6	36.3
60.9	62.8			47.3	39.9	32.7	28.7			
	61.9		50.7		41.0					
64.9	62.5	53.5	44.1	35.0	32.7					
0.110	61.6	52.5	43.3	35.4	28.8					
$R = CH_{2}$	-				•					
40.9	69.1		67.4			63.8	61.2	$58.5^{2b}$		
			66.9		65.7		63.8	58.1		53.5
50.9		68.0	64.0	58.2	1	53.1				
	72.2	69.1	63.3	59.7	55.0	]				
55.9	67.6	61.8	00.0	48.8	43.3					
00.0		61.9	47.7	1010						
R = Cl										
50.9	82.5		79.8	i İ	71.2		68.1	64.5		
	81.0		78.7		70.35		70.1	62.3	56.9	
55.9	77.0		70.5	69.3ª	64.95	60.8	55.8ª	1		
60.9	78.8	70.7	67.0	59.7	54.50					
	77.8	75.2	68.6	62.2ª	55.3∘					
				part B—	DNPH me	THOD				
R = H										
61.0 <sup>d</sup>	64.8		$55.4^{a}$		1	43.4		$32.4^{b}$		17.5
61.0*	59.1	53.4	47.0			27.9	1	10.5	4.626	
61.01		59.5	47.7		45.9	1	31.0			10.2
71.0	61.6	49.0	 	26.5	15.18		9.7	2.6		
Acetate				;						
61.0	91.2	78.3		62.4			34.3			
71.0	90.3	58.6	40.4		13.46		4.7			
$R = CH_3$										
51.0	74.8	1	69.7			55.1	1		1	24.4
61.0	76.6	63.8	50.8	<u> </u>		23.9				
$\mathbf{R} = \mathbf{Cl}$			 							
51.0	81.4		76.2			<b>55</b> .9ª		39.8		28.0
71.0	1	62.7			35.5	26.4	11.325			

TABLE IV RATE DATA OF ACETOPHENONE OXIMES. TIME IN HOURS; WEIGHT IN MILLIGRAMS OF OXIME

• = +0.25 hours; • = +0.5 hours; • = +0.75 hours. • = 93.6% H<sub>2</sub>SO<sub>4</sub>; • = 100% H<sub>2</sub>SO<sub>4</sub>; • = 96% for this and all other DNPH runs. The oxidation runs were with 95.5% H<sub>2</sub>SO<sub>4</sub>.

## PART II

A. Preparation of acetophenoxime-O-sulfonic acids (III a, b, and c). To a solution of 0.06 mole of chlorosulfonic acid (b.p.  $147-150^{\circ}/748$ ) in 75 cc. of ether (dried over  $P_2O_5$ ) in a three-necked flask protected with a calcium chloride tube was added dropwise a solution of 0.05 mole of oxime in 75 cc. of dry ether while stirring and cooling in an ice-bath. The oxime-O-sulfonic acid had finished separating after half an hour, and was filtered with slight suction and washed by successive resuspensions with a total of 500 cc. of dry ether in such a way that the solid was never allowed to become completely dry. It was then sucked dry for 5-10 seconds and immediately dried *in vacuo* over  $P_2O_5$ . The efficiency with which the products were protected from moisture during these operations determined the purity of the oxime-O-sulfonic acids, which were all white, free-flowing powders. The yields were: IIIa, 70%; IIIb, 75%; IIIc, 50%.

B. Reactions of p-methylacetophenoxime-O-sulfonic acid (IIIb). IIIb was the most stable of the acids; its m.p. was 84°, instantaneous decomposition when placed in bath at 80° otherwise 132-145°. Its acid equiv. by glass electrode titration was 204, 219.5 (two runs); calc'd; 229; undoubtedly, some hydrolysis had taken place during titration. IIIb was halogen-free by silver nitrate test. If exposed directly to air, IIIb deliquesced, but, if partly exposed, such as in a loosely-stoppered weighing bottle, its neutral equiv. changed in a period of 2 days to 126.8, 127.5 (calc'd for oxime salt, IIb: 123.5).

Rearrangement: IIIb (acid equiv.: 204, 0.012 mole) was suspended in 30 cc. of ethylene chloride and heated to 47° whereupon a spontaneous rearrangement began, which maintained itself at this temperature for 4 minutes. The solid was filtered (m.p. 147-153°), washed thoroughly with sodium bicarbonate solution and dried. Yield: 80% *p*-methylacetanilide; m.p. 144-148.5°; recrystallized from alcohol, m.p. 149-150.5°; mixed m.p. with authentic sample 149-151°. Attempted rearrangement of IIb (acid equiv.: 127.5) under the same conditions, except that the ethylene chloride suspension was refluxed, yielded 91% *p*-methylacetophenoxime, m.p. 81-87°, recrystallized from alcohol m.p. 86-88°; mixed m.p. with authentic sample 86-88°. Attempts to run an aqueous rearrangement of IIIb failed; only *p*-methylacetophenone was obtained.

Reaction with concentrated  $H_2SO_4$ : IIIb (1 g.) was carefully dissolved in 6 cc. of mechanically stirred 96% sulfuric acid maintained at 32-33°. After 10 min. the mixture was poured on ice, neutralized with sodium hydroxide, and allowed to cool overnight. The yield was 0.55 g. (85%) of crude *p*-methylacetophenoxime, m.p. 79-81°, recrystallized from cyclohexane, m.p. 85-87°. Similarly, IIIb, dissolved in H<sub>2</sub>SO<sub>4</sub> at 43-45°, yielded 84% of a mixture of oxime and *p*-methylacetanilide of which at least 50% was the amide (separated by cyclohexane). More amide is thus formed than expected from rearrangement of the oxime. However, local heating effects were noticeable especially if IIIb was introduced into the sulfuric acid in portions larger than 0.1 g.

C. Reactions of acetophenoxime-O-sulfonic acid (IIIa). IIIa was the most reactive of the acids; it could only be dried in a desiccator with  $P_2O_5$  by cooling desiccator to ice temperature before evacuation. IIIa melted at 80°, instantaneous decomposition if placed in bath at 78°. Its acid equiv. was 202; cale'd: 215. The oxime salt (IIa) was an oil.

Rearrangement: IIIa (0.012 mole) was suspended in 30 cc. of ethylene chloride. A spontaneous reaction began at 40° and maintained itself (with external cooling), at  $40-45^{\circ}$  for 10 minutes. After washing with bicarbonate solution, a 70% yield of acetanilide was obtained, m.p. 101-109°, recrystallized from cyclohexane m.p. 114-115°. The method was quite adaptable to large scale preparations of amides by the Beckmann rearrangement: the oxime (0.06 mole) was added to chlorosulfonic acid (0.075 mole) dissolved in 100 cc. of ethylene chloride. The flask was heated cautiously to the point where the internal temperature exceeded the external one by a few degrees. Cooling was sometimes necessary. After the usual purification, a yield of approximately 0.05 mole of amide was obtained.

Hydrolysis: IIIa (1 g.) was dissolved in 96% sulfuric acid which was well stirred and maintained at 23-25° during addition. After 10 minutes reaction, the mixture was poured on to ice and neutralized with NaOH solution. An 80% yield of acetophenoxime was ob-

tained. Similarly, IIIa in  $H_2SO_4$  at 45-46° for 10 minutes yielded 83% acetophenoxime and no amide. Rather than continue this study with an unstable acid, it was instead converted to the potassium salt by neutralization with aqueous KHCO<sub>3</sub>. This product and the one obtained by the method of Smith (18) were identical (m.p. 210-211°, dec., considerable previous sintering; m.p. 152° with resolidification when placed in a bath at 150°; the latter m.p. was erratic but was always sharp).<sup>2</sup> The potassium salt (2 g.) was dissolved in 10 cc. of  $H_2SO_4$  under conditions given below and yields of oxime or amide found.

H2SO4, %	т°С	TIME	% OXIME	% AMIDE
Management in a second statement of the second stateme		min.		
96	10.0	12	83	0
96	25-30	7	65	5
96	40-45	9	47	28
100	26-28	4	91.5	0

D. Reactions of p-chloroacetophenoxime-O-sulfonic acid (IIIc). IIIc was most hygroscopic of the acids. Its m.p. was 87.5°, dec. when placed in bath at 80°. Its acid equiv. was 239.5, 239.5; calc'd: 249.5.

Rearrangement: IIIc (0.016 mole) was suspended in 30 cc. of ethylene chloride. Spontaneous rearrangement did not begin till 56°, whereupon the temperature rapidly rose to 62-63° and maintained itself for 2 minutes. During this time, the solid changed to an oil. After treatment with bicarbonate solution and the usual purification, p-chloroacetanilide (m.p. 178.5-180°, mixed m.p. with authentic sample 179-181°) was obtained in 84.5% yield. IIIc was also hydrolyzed to p-methylacetophenoxime in 85% yield by dissolving in water and allowing it to stand for several days (m.p. 83-94°; recrystallized from cyclohexane, m.p. 97-98°).

#### SUMMARY

Some generalizations on the mechanism of the Beckmann rearrangement have been summarized. A method of analysis of the oxime in the presence of its rearrangement product has been developed to facilitate kinetic studies of the rearrangement of oximes in sulfuric acid. The results confirmed the generality that alkyl substituted acetophenone oximes rearrange faster than acetophenoxime which, in turn, rearranges faster than electronegatively-substituted acetophenone oximes. The possibility of ester formation as an intermediate in the rearrangement has been studied by synthesis and characterization of the acetophenoxime-O-sulfonic acids. Their properties suggest that the rate-determining step is either ester formation or a similar step involving a lower activation energy level than that of ester formation, such as loss of water from the oxime salt. It is not possible from the experimental evidence to decide which of these steps was the truth. In any event, the rate of formation of rearranged product is determined by either one or both of these steps and not by the actual migration of the aryl or alkyl group.

NASHVILLE 4, TENN.

<sup>&</sup>lt;sup>2</sup> The difficult recrystallizations of the potassium salt by Smith (18) were unnecessary, as it could be suspended in boiling alcohol and triturated with water until dissolved, filtered while hot, and then cooled. The salt crystallized with 0.5 mole of water which was removed in Abderhalden dryer at 100° and at low pressure. Calc'd for  $C_8H_8NO_4SK$ : C, 37.9; H, 3.16; S, 12.63. Found: C, 37.77; H, 3.36; S, 13.0. The drying process raised the m.p. 152° when placed in a bath at 150° to approximately 192° (sudden immersion).

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