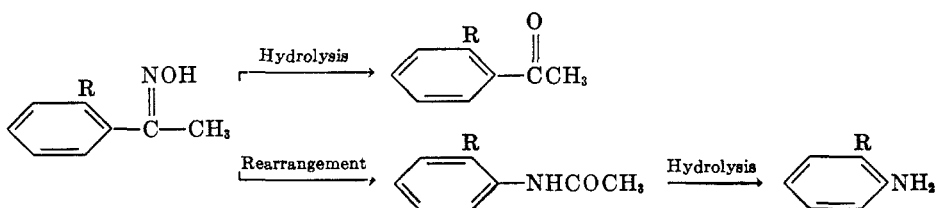


THE BECKMANN REARRANGEMENT. V. THE REARRANGEMENT RATES OF SOME *ortho*-SUBSTITUTED ACETOPHENONE OXIMES (1)D. E. PEARSON AND W. E. COLE¹*Received November 29, 1954*

In 1925 von Auwers and co-workers (2) reported a very unusual chemical property of some *ortho*-substituted acetophenone oximes. Of a list of 35 aromatic oximes, approximately half rearranged in 30–100% yields to the corresponding amides (isolated as the amines) in the presence of 17% aqueous hydrochloric acid. In this medium, exclusive hydrolysis to the ketone would be anticipated.



The extremes of divergence in this series may be represented by 2-iodoacetophenone oxime which gave only ketone and by 2,4-dimethyl-6-methoxyacetophenone oxime which gave a quantitative yield of rearrangement product. von Auwers was unable to explain these results and specifically stated that steric hindrance could not be the cause of this unusual phenomenon. Lachman (3) also reported the rearrangement of benzophenone oxime in 67% yield by means of aqueous hydrochloric acid, although the water content was limited to 10% by weight, and although the temperature of rearrangement was rather high (150°). The yield of rearrangement product was further increased by the addition of hydroxylamine hydrochloride. It is obvious that both of these workers actually studied competitive reactions in which rates of hydrolysis *versus* rates of rearrangement determined the products. von Auwer's data strongly suggest that the rates of rearrangement of some *ortho*-substituted acetophenone oximes are accelerated—a point which would probably give further insight into the mechanism of rearrangement, provided a direct comparison could be made with rates of other acetophenone oximes. The investigation of the comparative rates was therefore undertaken in this laboratory.

The rates of rearrangement of the oximes in concentrated sulfuric acid were followed, as previously described (4), by the gravimetric determination of the 2,4-dinitrophenylhydrazones derived from the unchanged oximes. The rates were first order with respect to the oxime concentrations, although the constants are less precise than those previously recorded. The results are given in Table I.

The data show that the *ortho*-substituted groups greatly accelerate the rates of rearrangement of the acetophenone oximes, as was anticipated from the work

¹ Taken from the Ph.D. thesis of W. E. Cole, Vanderbilt University, 1955.

TABLE I
RATE CHARACTERISTICS OF THE REARRANGEMENT OF *ortho*-SUBSTITUTED
ACETOPHENONE OXIMES IN SULFURIC ACID

Oxime ^a	t, °C.	k ^b × 10 ³	t ^c ½	E _A ^d	ΔS ^e
<i>o</i> -Methyl	25.0	11.41 ± 1.33	61	20.65	-6.3
	30.0	20.27 ± 1.81	34		
<i>o</i> -Chloro	40.9	3.27 ± 0.14	212	24.1	-1.2
	50.9	10.81 ± 0.22	64		
		k ^b × 10 ⁵			
<i>o</i> -Nitro	40.9	4.77 ± 0.36	14,500	27.2	-2.4
	50.9	18.39 ± 0.81	3,770		

^a Concentration: 0.001 mole in 10.0 ml. of 94.5% sulfuric acid (Merck). ^b First order rates in reciprocal minutes; ± refers to the standard deviation. ^c Minutes. ^d Kilocalories. ^e Entropy units.

of von Auwers (2). On the assumption that the electrical effect of the group is approximately the same in the *ortho* as in the *para* position (5), the ratio of the *ortho* to the *para* rates gives a rough assessment of the steric effect:

o-Methyl/*p*-methyl (6) rate: 107

o-Chloro/*p*-chloro (6) rate: 15

o-Nitro/*p*-nitro (6) rate: 6

In fact, the rate of rearrangement of *o*-methylacetophenone oxime was so fast that it could only be measured near room temperature rather than at the usual temperature of 51°.

The results of von Auwers can thus be traced primarily to steric acceleration by *ortho*-substituted groups and, more accurately, to a unique dual character of the steric effect. The steric effect both accelerates the rate of rearrangement and decelerates the rate of hydrolysis. If one takes into account the electrical effects of the *ortho* groups also, all the data of von Auwers seem quite understandable. For example, in 2-iodoacetophenone oxime, the electrical effect of the bulky iodine atom evidently slows down the rate of rearrangement and accelerates the rate of hydrolysis to such an extent that the steric acceleration of rearrangement is not evident. In 2,4-dimethyl-6-methoxyacetophenone oxime, all steric and electrical factors presumably accelerate the rate of rearrangement and decelerate the rate of hydrolysis.

In regard to the mechanism of rearrangement, the steric effect undoubtedly operates by preventing coplanarity between the benzene ring and the α -oximinoethyl grouping ($-\text{C}=\text{NOHCH}_3$). Physical evidence in support of this view is given in the following paper (7). Chemical evidence is provided by the fact that *o*-methoxyacetophenone oxime can be sulfonated with extraordinary ease at room temperature in comparison with other unhindered oximes, ketones, or even the parent ketone, *o*-methoxyacetophenone. The abnormal rate of sulfonation of the oxime precluded the determination of the rate of rearrangement in sulfuric acid. The most appealing interpretation is that the resonance interaction

between the ring system and the α -oximinoethyl grouping which normally deactivates the ring system toward electrophilic reagents is diminished to such an extent that the oxime is sulfonated in a manner similar to a hydrocarbon rather than to an aromatic ketone. Coplanarity between groups must still exist in *o*-methoxyacetophenone, however, since this ketone is sulfonated at a more nearly normal rate.

The loss of coplanarity between the groupings in the *ortho*-substituted acetophenone oximes does not in itself explain the steric acceleration of rates. The explanation may be that the ring system is more susceptible to bonding with the electron-deficient nitrogen atom when resonance interactions are diminished. Another hypothesis suggests itself also. The explanation may be that one of the initial steps in the rearrangement of *any* acetophenone oxime is the twisting of the α -oximinoethyl grouping out of the plane of the ring so that the nitrogen and carbon atoms pictured are equidistant above and below the plane of the ring:

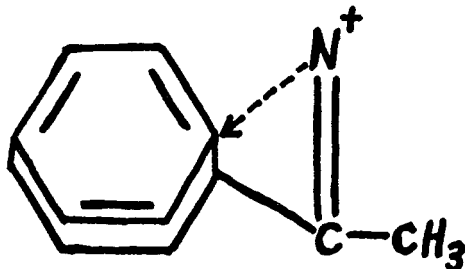


FIG. 1

The process of nitrogen-ring bond formation and carbon-ring bond breaking is thus facilitated. In *ortho*-substituted acetophenone oximes the twisting out of the plane of the ring is already accomplished, and the energy required for activation may therefore be diminished. It is possible to test the latter hypothesis, and such a test is under investigation.

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EXPERIMENTAL

All melting points are corrected and boiling points are uncorrected. Most of the oximes reported in the following sections are prone to decompose on standing. They were stored in separate desiccators over solid potassium hydroxide. A decomposition product, probably nitrogen dioxide, catalyzes the decomposition of the remaining oxime. The usual behavior of the oximes, therefore, is that they remain unchanged for weeks, or for even months, but then rapidly turn yellow, sinter or liquefy, and evolve gas of an acidic nature.

o-Methylacetophenone and derivatives. The ketone was prepared from *o*-tolunitrile (1 equiv., b.p. 57° at 2 mm., n_D^{25} 1.5263) and methylmagnesium iodide (3 equiv.) in a manner previously described (8). The yield was 74% of a colorless oil, b.p. 67° at 3 mm., n_D^{25} 1.5303; reported (9) n_D^{20} 1.5325. The oxime was prepared by the method of Pearson and Bruton (4) and recrystallized repeatedly from petroleum ether (b.p. 30–60°): large, transparent prisms, m.p. 64.5–65.5°, reported (2, 10) 61.5–63°. The 2,4-dinitrophenylhydrazone, obtained from rate studies and recrystallized once from ethanol-ethyl acetate, gave light orange plates:

m.p. 164–166°, reported (9) m.p. 161–162°. The Beckmann rearrangement of the oxime (1.5 g.) in 10 ml. of sulfuric acid at 30° for 8 hours yielded *o*-acetotoluidide: 100% crude yield, m.p. 104.5–106°; recrystallized from methanol, m.p. and mixture m.p. with an authentic sample 109.5–110°.

o-Chloroacetophenone and derivatives. The ketone was prepared from *o*-chlorobenzonitrile (m.p. 43–44°) and excess methylmagnesium iodide as previously described (8). The yield was 45% of colorless oil: b.p. 83.5–84° at 2 mm., n_D^{25} 1.6844; reported (11) n_D^{25} 1.6850. The oxime, recrystallized repeatedly from methylcyclohexane, melted at 114–115° (slight previous sintering); reported (2) m.p. 103° which changed to 112–113° on recrystallization from hot water. The change in melting point, which may be indicative of polymorphic forms, was also observed in this laboratory. The low-melting form (104.5–105.5°) was obtained by rapid cooling of a petroleum ether (b.p. 70°) solution. The 2,4-dinitrophenylhydrazone, obtained from rate studies and recrystallized from ethyl acetate, formed yellow orange plates, m.p. 209–211°, reported (12) m.p. 206°. The Beckmann rearrangement of the oxime in sulfuric acid gave *o*-chloroacetanilide: 90% crude yield, m.p. 86–88° (previous sintering); after recrystallization from methylcyclohexane, the m.p. and mixture m.p. with an authentic sample was 86–87°.

o-Nitroacetophenone and derivatives. The ketone was made by the method of Reynolds and Hauser (13): 75% yield, b.p. 122–124° at 2 mm. The oxime, prepared as in Reference 4 and recrystallized repeatedly from aqueous methanol, was obtained as needles with a faint green tinge: m.p. 115.5–116.5°; reported (14) m.p. 117°. There were indications that both *syn* and *anti* forms of the oxime could be obtained. The 2,4-dinitrophenylhydrazone, obtained from rate studies and recrystallized once from ethyl acetate, was isolated as orange needles, m.p. 182.5–184° when immersed at 140°. The reported melting points are quite variable because of the dependence on temperature of immersion: m.p. 168–170° (14); m.p. 152–154° (15). The authors of the latter reference also report difficulty in making the oxime from the ketone; no such difficulty was experienced in this laboratory. Beckmann rearrangement of the oxime yielded *o*-nitroacetanilide, 86%, m.p. 84–88°. After two recrystallizations from aqueous ethanol, the m.p. and mixture m.p. with authentic sample was 91–92°.

o-Methoxyacetophenone and derivatives. The ketone was prepared from *o*-methoxybenzonitrile, b.p. 97° at 1 mm., and excess methylmagnesium iodide as previously described (8): 64% yield, b.p. 109–110° at 2 mm., n_D^{25} 1.5365; reported (16) n_D^{25} 1.5379. An erroneous refractive index has been recently reported (17). The oxime, prepared in the usual manner (4), was carefully examined for an isomer by fractional crystallization from methylcyclohexane, but none was found. The yield of fern-like, colorless crystals was 100%, m.p. 95–96° (slight cloudiness in melt, and m.p. somewhat dependent on temperature of immersion); reported (2) m.p. 83°. Hypobromite oxidation (18) of a small sample of oxime yielded lustrous plates of *o*-methoxybenzoic acid: 44%, m.p. 95.5–98.5°, reported m.p. 98–99°; bromination of the acid yielded 5-bromo-2-anisic acid, m.p. 120–120.5°, reported m.p. 119–120°. The 2,4-dinitrophenylhydrazone of the ketone, recrystallized from ethyl acetate, was isolated as orange plates, m.p. 194–196°; reported (19) m.p. 196–198° and also (17) 185°.

The attempted Beckmann rearrangement of *o*-methoxyacetophenone oxime. Difficulty was encountered in determining the rate of rearrangement of this oxime. The weights of the 2,4-dinitrophenylhydrazone precipitates actually increased when successive aliquots of the oxime, subjected to rearrangement, were analyzed. These data indicated that a carbonyl compound remained throughout the rearrangement. Furthermore, the precipitate of the 2,4-dinitrophenylhydrazone did not resemble that of *o*-methoxyacetophenone. The rate studies of this oxime were therefore abandoned, and efforts were directed toward solving the puzzling aspects of this problem. After several trial runs, it was found advantageous to isolate the 2,4-dinitrophenylhydrazone of the unknown compound as follows: 3 g. of *o*-methoxyacetophenone oxime was dissolved in 15 ml. of cold, concentrated sulfuric acid and allowed to stand at room temperature for 48 hours. The mixture then was poured into ice and water. 2,4-Dinitrophenylhydrazine (3.6 g.), previously dissolved in a hot solution of

100 ml. each of concentrated hydrochloric acid, water, and ethanol, was added all at once to the diluted reaction mixture. Cooling resulted in a bright orange precipitate which was removed by filtration and washed with water—yield after air-drying 4.5 g. The compound (2.35 g.) was recrystallized from a mixture of 200 ml. of methanol, 50 ml. of water, and 5 ml. of hydrochloric acid (the latter to prevent 2,4-dinitrophenylhydrazine from depositing) using a hot filtration. Orange-colored, small crystals came out slowly, 1.3 g., m.p. 211.5–212° (gas, dec., lightens in color before melting). The acidic character and analysis indicated that the oxime had been sulfonated, rather than been rearranged, and that the isolated product was the 2,4-dinitrophenylhydrazine salt of 2-methoxy-5-sulfoacetophenone-2,4-dinitrophenylhydrazone.

Anal. Calc'd for $C_{21}H_{20}N_4O_{12}S$: N, 18.42; Neut. equiv., 608.5.

Found: N, ² 18.07; Neut. equiv., 611.

Confirmation of this structure was undertaken by synthesis from *o*-methoxyacetophenone rather than from the oxime. It was surprising that under identical conditions for sulfonation of the oxime, the ketone was not sulfonated. The sulfonation, however, was accomplished as follows: 1.94 g. of *o*-methoxyacetophenone was dissolved in 15 ml. of cold 99.6% sulfuric acid and turned deep red in color. After 30 minutes at 70°, sulfonation was incomplete, since an aliquot diluted with water gave an insoluble oil. After a further 90 minutes, during which time the oil-bath temperature was raised from 70° to 105°, the sulfonation was complete. The solution was poured into ice and water with stirring. 2,4-Dinitrophenylhydrazine was added in the manner and in the proportions used in isolating the product from the sulfonation of the oxime. The yield of bright orange crystals was 77%, m.p. 211.5° (gas, dec., lightens before melting); the mixture m.p. with the sample obtained from the oxime was undepressed; neutral equivalent 617, calc'd: 608.

Thus, it has been shown that *o*-methoxyacetophenone oxime is sulfonated in sulfuric acid at room temperature without being rearranged and that the ketone is not sulfonated appreciably under the same conditions.

Rates of rearrangement. The rates were followed, as previously described (4), by gravimetric determination of the 2,4-dinitrophenylhydrazones derived from the unchanged oximes. The preferred colorimetric procedure (1) had not been developed at the time of this investigation. Because of the physical properties of the *ortho*-substituted 2,4-dinitrophenylhydrazones (*e.g.*, lower melting-points and greater solubilities), the determinations are less precise than those of former studies (4, 6). Several modifications were necessary to obtain even this precision: the oximes dissolved in sulfuric acid were diluted with 100 ml. rather than 20 ml. of water and the suspensions were digested with 2,4-dinitrophenylhydrazine for five rather than two hours; the precipitates were dried at 80° rather than 110°. A greater number of analytical samples was also run both for the calibration curves and for the rate determinations. The calibration determinations were run on samples of each oxime ranging in weight from 0.0005 to 0.001 mole, as encountered in the rate studies. The precision was as follows for the substituted acetophenone oximes:

o-Methyl. $99.11 \pm 0.86\%$; correction factor 1.009; no trend in yields of 2,4-dinitrophenylhydrazone between 0.0010 and 0.0005 mole of oxime.

o-Chloro. Between 0.00075 and 0.001 mole of oxime: $99.71 \pm 0.09\%$; correction factor 1.0029. Between 0.0005 and 0.00075 mole of oxime: $98.88 \pm 0.14\%$; correction factor 1.0113.

o-Nitro. Between 0.00075 and 0.001 mole of oxime: $99.94 \pm 0.29\%$; correction factor 1.0006. Between 0.0005 and 0.00075 mole of oxime: $98.81 \pm 0.20\%$; correction factor 1.0120.

o-Methoxy. $98.18 \pm 0.60\%$; correction factor 1.0185. No trend in yields. These data were not used because of sulfonation of the oxime during the time of rearrangement.

The correction factors were used to correct the weights of the 2,4-dinitrophenylhydrazones obtained during the rate determinations. The rates were first order with respect to the oxime concentrations and are given in Table I.

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SUMMARY

The rates of rearrangement of *o*-methyl-, *o*-chloro-, and *o*-nitro-acetophenone oximes were determined; they were found to be extraordinarily fast. This result is attributed to loss of coplanarity between the ring system and the α -oximino-ethyl grouping. The rate of rearrangement of *o*-methoxyacetophenone oxime could not be determined because of its rapid sulfonation in sulfuric acid.

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