Substituent Effects in the Lossen Rearrangement of Benzoyl Acylhydroxamates[1a]

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The rates and kinetic parameters of Lossen rearrangements of sodium salts of a series of benzoyl acylhydroxamates have been determined. The results are discussed in terms of polar and steric effects of substituent groups.

The rates of rearrangement reactions are influenced by proximal and nonproximal substituents of a migrating group. The effects of such proximal substituents are of special interest. *ortho*-Substituted phenyl groups migrate slower than the corresponding *para* derivatives in acid-catalyzed rearrangement of symmetrical aromatic pinacols.[2a] Examples of rate acceleration are known: *ortho*-substituted benzoic acids react with hydrazoic acid (the Schmidt reaction) faster than do the *meta* and *para* derivatives,[2b] the Curtius reaction proceeds more rapidly with *ortho*-substituted benzazides than with the *meta* and *para* isomers,[3] and *ortho* derivatives of the potassium salts of acylated benzohydroxamic acids in alkaline media undergo the Lossen rearrangement faster than do the corresponding *meta* and *para* compounds.[4]

A rate study of the effect of substituents of the migratory group in the Lossen rearrangement (eq. 1) in the aliphatic series (R = alkyl) was undertaken to learn if the substituent effects are the same or different from those observed in the aromatic series (R = aryl).

$$\mathrm{RCONHOCOPh} \xrightarrow[-\mathrm{H_2O}]{\mathrm{NaOH}} \mathrm{RC\bar{N}OCOPh} \xrightarrow{\mathrm{Na^+}} \mathrm{RN{=}C{=}O + PhCO_2Na} \quad (1)$$

The rates of rearrangement of a series of sodium benzoyl acylhydroxamates (R = alkyl) have now been measured in 0.093 *N* aqueous ammonia solution[5]; a colorimetric method for following the concentration of the benzoyl acylhydroxamates also has been developed.[6] First-order kinetics with respect to sodium benzoyl acylhydroxamate were observed in all instances. The results are summarized in Table I.

TABLE I

KINETIC RESULTS[a] FOR LOSSEN REARRANGEMENT OF $Na^+[RCONOCOC_6H_5]^-$ IN 0.093 *N* AMMONIA

R	CH_3-	CH_3CH_2-	$(CH_3)_2CH-$	$(CH_3)_3C-$
$10^6 k_1$, 20°[b]			35.3	31.1
30°		11.3	178	149
40°	<1.6[f]	54.0		
Relative Rates,[c] 40°	<0.03[f]	1.00	14.9	12.0
ΔH^*[d]		29.2	28.0	27.1
ΔS^*[e]		+15.1	+16.6	+13.3

[a] First-order constants, sec.$^{-1}$, average of three determinations. Average deviation from the mean is less than 2% except for R = $(CH_3)_3C$, 30°, 2.5%; R = CH_3CH_2, 40°, 5.6%; and R = CH_3, 8.9%. [b] Accurate to ±0.05° except for determinations for R = CH_3, ±0.1°. [c] Values for R = $(CH_3)_2CH$ and $(CH_3)_3C$ were calculated from the rate constants calculated from activation parameters by means of the usual equation (see ref. 21). [d] Enthalpy of activation, kcal./mole. [e] Entropy of activation, cal./deg. mole, calculated from rate constants at 30° and ΔH^*. [f] These are maximum values (see ref. 9).

Equation 2 represents the accepted mechanism[4,5,7,8] of the Lossen rearrangement; migration of R from carbon to nitrogen probably occurs simultaneously with

$$\mathrm{RC\bar{N}OCOR'} \longrightarrow \left[\begin{array}{c} \mathrm{O} \\ \| \\ \mathrm{C} \\ \diagup \quad \diagdown \\ \mathrm{R}\text{-----}\mathrm{N}\text{-----}\mathrm{O{-}CO{-}R'} \end{array}\right]^- \longrightarrow \underset{\mathrm{I}}{} \quad \mathrm{RN{=}C{=}O + R'CO_2^-} \quad (2)$$

the heterolytic cleavage of the hydroxamate anion. Reaction of the intermediate isocyanate with water, ammonia, or the amine from hydrolysis of the isocyanate yields the observed products. Electron-donating substituents in R and electron-withdrawing substituents in R′ increase the rate of the Lossen rearrangement when R and R′ are *meta*- or *para*-substituted aryl groups.[4]

Inspection of Table I reveals that, as R is progressively changed from methyl[9] to *t*-butyl, the rate of the reaction increases except for the change from R = isopropyl to *t*-butyl. The electron-donating polar effect of the added methyl groups is expected to facilitate the rearrangement in agreement with the results obtained with aromatic systems.[4] A rate increase of at

(1) (a) A major portion of this research was completed while D. C. B. was a National Science Foundation Postdoctoral Fellow at The Ohio State University, January–August, 1962; (b) to whom inquiries should be directed, Western Michigan University.

(2) (a) W. E. Bachmann and F. H. Moser [*J. Am. Chem. Soc.*, **54**, 1124 (1932)] have listed the migratory aptitudes for this rearrangement; (b) M. E. D. Hillman, Ph.D. dissertation, The Ohio State University, Columbus, Ohio, 1958.

(3) Y. Yukawa and Y. Tsuno, *J. Am. Chem. Soc.*, **80**, 6346 (1958).

(4) R. D. Bright and C. R. Hauser, *ibid.*, **61**, 618 (1939).

(5) W. B. Renfrow, Jr., and C. R. Hauser [*ibid.*, **59**, 2308 (1937)] and Bright and Hauser[4] found that hydrolysis of the aroyl acylhydroxamates to the corresponding acylhydroxamic and arylcarboxylic acids is minimal when the Lossen rearrangement is carried out in 0.1 *N* aqueous ammonia. The compounds in the present study, except sodium benzoyl acetohydroxamate, undergo the Lossen rearrangement as fast as or faster than the compounds previously studied in 0.1 *N* ammonia solution.[4] Therefore, since variation in R (eq. 1) should have little effect upon the hydrolytic cleavage of the benzoyl group whether R is alkyl or aryl, except for variation in steric hindrance to hydrolysis in certain less favored conformations, hydrolysis of the compounds in the present study is minimal except with sodium benzoyl acetohydroxamate which may hydrolyze at a rate comparable to its rate of rearrangement (see ref. 9).

(6) Previous workers[5] obtained a rate constant of 0.00138 min.$^{-1}$ for rearrangement of potassium benzoyl benzohydroxamate at 30° in 0.10 *N* ammonia using a gravimetric procedure. By the method of the present study a value of 0.00109 min.$^{-1}$ at 30° in 0.093 *N* ammonia was obtained. Similarly, the rate constants obtained in the previous study[4] for $K[RCONOCOC_6H_5]$ where R = cyclohexyl and 2-phenylethyl are of the same magnitude as the rate constants obtained in the present study for $Na[RCONOCOC_6H_5]$ where R = isopropyl and ethyl, respectively.

(7) J. Hine, "Physical Organic Chemistry," 2d Ed., McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p. 335.

(8) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, pp. 498–502.

(9) The rate constant in Table I for R = CH_3 is a maximum possible value for the Lossen reaction and is a combination of rates of the Lossen reaction and hydrolysis of sodium benzoyl acetohydroxamate to acetohydroxamic acid and sodium benzoate and/or to sodium acetates and benzoates and hydroxylamine. Acetohydroxamic acid in 0.093 *N* aqueous ammonia at 40° is destroyed (measured colorimetrically) about half as fast as sodium benzoyl acetohydroxamate reacts under the same conditions.

least 33-fold occurs for the change from R = methyl to ethyl and an increase of 15-fold for the change R = ethyl to isopropyl. Little steric effect seems likely for the change from methyl to ethyl; the difference in rates is ascribed to the polar effect of the added methyl group. The smaller rate increase for the change from ethyl to isopropyl than from methyl to ethyl and the actual decrease in rate for the change from isopropyl to *t*-butyl is probably due to steric effects operating to reduce the rate of reaction. At least two modes of operation of such steric effects can be visualized if the transition state of the rearrangement can be represented as in I. Considerable bond breaking between the nitrogen and oxygen in the transition state will account for the observed polar effects. The two steric effects are greater hindrance to solvation in the transition state than in the initial state, and kinetic-energy steric effects, *i.e.*, greater hindrance to internal motions in the transition state than in the initial state.[10] Both of these steric effects operate in the same direction. Taft,[11] in his work on the separation of polar, steric, and resonance effects, found that the polar effects of successive α-methyl substitution are approximately additive while the steric effects are not, but instead accumulate at an increasing rate with successive α-methyl substitution. The results of the present study seem consistent with that view.

A rate-accelerating steric effect as observed in the Schmidt,[2b] Curtius,[3] and Lossen[4] reactions of *ortho*-substituted phenyl systems is possible if transition state I lies close to products; this effect is minor, however, compared to the other steric effects in the present system.

The steric effects of *ortho* substituents in the Schmidt,[2b] Curtius,[3] and Lossen[4] reactions of aromatic systems in general increase the rates of reaction. In the Lossen reaction of the aliphatic derived compounds reported herein, however, the steric effects of the α-substituents appear to have the opposite effect.

Experimental

Neutralization equivalents were determined in aqueous ethanol solution with phenolphthalein as indicator. All monohydroxamic acids gave a maroon color with aqueous ferric chloride.

The monohydroxamic acids or their salts were prepared by adaptation of previous methods[5,12]: acetohydroxamic acid, m.p. 89.5–91.0°, lit.[12a] 88–89°; propionohydroxamic acid, obtained as its potassium salt which was converted directly to benzoyl propionohydroxamate; isobutyrohydroxamic acid, m.p. 116.5–117.3°, lit.[12b] 116°; pivalohydroxamic acid, m.p. 163.6–164.1° dec. (*Anal.* Calcd. for $C_5H_{11}NO_2$: N, 11.95. Found: N, 12.0).

The benzoyl acylhydroxamates were prepared by adaptation of a previous method[13]: benzoyl acetohydroxamate, m.p. 97–99° (lit.[12a] 98–99°), neut. equiv. 173 (calcd. 179); benzoyl propionohydroxamate, m.p. 114.1–114.9° (lit.[13] 115–116°), neut. equiv. 197 (calcd. 193); benzoyl isobutyrohydroxamate, m.p. 145.2–146.4° (lit.[12b] 148°), neut. equiv. 212 (calcd. 207); benzoyl pivalohydroxamate, m.p. 105.8–107.0° (*Anal.*[14] Calcd. for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33; neut. equiv., 221. Found: C, 64.98; H, 6.80; N, 6.25; neut. equiv., 233).

Sodium Salts of Benzoyl Acylhydroxamates.—These kinetic reagents were prepared by a method similar to that used previously.[12a,b,13] Separate solutions of equivalent amounts of the benzoyl acylhydroxamate and sodium hydroxide were prepared in minimum amounts of methanol, cooled to *ca.* −10°, and mixed. Addition of ether to the solution precipitated the salt, which was removed by filtration and stored in a freezer (−20°) after a brief atmospheric drying period.

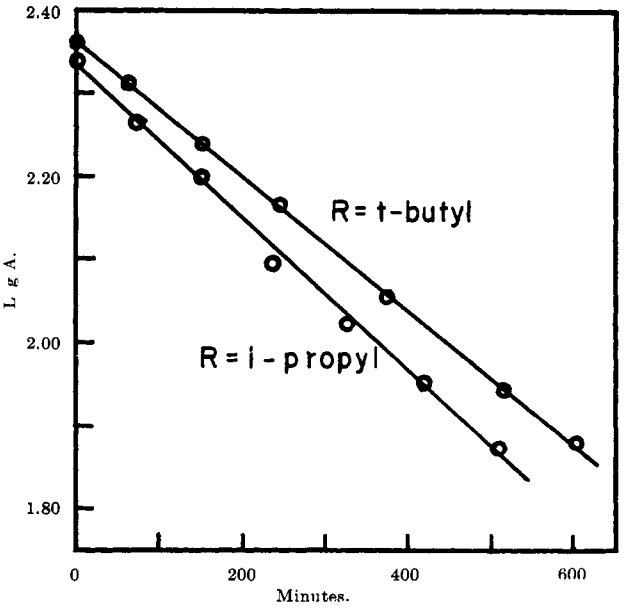

Fig. 1.—Typical rate data at 20° for Na[RCONOCOC$_6$H$_5$].

N-Alkylureas.—Approximately 0.025 *M* solutions (except the propiono derivative, 0.012 *M*) in 0.1 *N* ammonia of the sodium salts of benzoyl propiono-, isobutyro-, and pivalohydroxamates were allowed to stand for sufficient time to ensure complete reaction (in some cases the reaction mixtures from the kinetic runs on a compound were combined and worked up). The solutions were evaporated to dryness *via* an air current or under reduced pressure at 40° or less. The residue was extracted with hot benzene or ethyl acetate and the urea then crystallized from the extraction solvent. The infrared spectra were consistent for the ureas.

N-Ethylurea, 19% yield (crude), was recrystallized to m.p. 90–92°, lit.[15] 92.1–92.4°. N-Isopropylurea, 33% yield (crude), was recrystallized to m.p. 151.1–152.1°, lit.[16] 154°. When the reaction was run in 1 *N* ammonia, a 61% yield was obtained.

N-*t*-Butylurea, 32% yield, had m.p. 177.2–178.2° dec., lit.[17a] 172° dec., lit.[17b] 183° dec. A sample from another reaction had m.p. 180.5–181.5° dec. and no depression when mixed with the first sample. When the reaction was run in 1 *N* ammonia, a 40% yield was obtained.

Kinetic Methods and Calculations.—It has been shown[18] that benzoyl benzohydroxamate is converted almost entirely into benzhydroxamic and benzoic acids by heating with 3–6 *N* sodium hydroxide. A variant of this method was adopted for the conversion of the benzoyl acylhydroxamates into the monohydroxamic acids, which react with ferric chloride to produce colored complexes suitable for colorimetric analysis.[19] Beer's law is obeyed within the estimated accuracy of the colorimeter and the aliquot measure.

The initial concentration of the alkali salts of the benzoyl acylhydroxamates in all kinetic runs was 0.0250 *M* except for one run with sodium benzoyl acetohydroxamate in which it was 0.0500 *M*. All solutions were prepared by adding a weighed sample of the sodium benzoyl acylhydroxamate to an aliquot of 0.093 *N* ammonia.

(10) R. W. Taft, Jr., "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p. 652 ff.

(11) Ref. 10, pp. 600–602.

(12) (a) L. W. Jones, *Am. Chem. J.*, **20**, 1 (1898); (b) L. W. Jones and A. W. Scott, *J. Am. Chem. Soc.*, **44**, 407 (1922).

(13) L. W. Jones and L. Neuffer, *ibid.*, **39**, 659 (1917).

(14) Galbraith Laboratories, Inc., Knoxville, Tenn.

(15) T. L. Davis and K. C. Blanchard, *J. Am. Chem. Soc.*, **51**, 1797 (1929).

(16) A. Conduche, *Ann. chim. phys.*, [8]**13**, 66 (1908).

(17) (a) A. Schneegans, *Arch. Pharm.*, **231**, 677 (1893); (b) M. Brander, *Rec. trav. chim.*, **37**, 83 (1918).

(18) E. Mohr, *J. prakt. Chem.*, [2]**71**, 133 (1905).

(19) It is not necessary that the conversion be 100% complete in order to be sure that the absorbance is proportional to the concentration of benzoyl acylhydroxamate, but rather that the conversion proceeds to the *same per cent* completion each time the procedure is carried out. The latter is the case in the present study since the conditions used for the conversion make the process a strictly pseudo-first-order process.

Procedure.—A 1-ml. aliquot of the reaction mixture was pipeted into a 50-ml. volumetric flask containing a 5-ml. aliquot of aqueous sodium hydroxide (20 g. per 100 ml. of water) and the flask was heated for 10 min. on a steam bath. The flask was cooled and 2.3 ml. of concentrated hydrochloric acid was added in portions with intermittent cooling. A 25-ml. aliquot of aqueous ferric chloride solution (≥0.5 g. per 300 ml. of water plus several drops of concentrated hydrochloric acid) was added and the flask diluted to the mark with distilled water. The absorption of the solution was then immediately measured with a Klett-Summerson photoelectric colorimeter; the blank solution consisted of a 25-ml. aliquot of the ferric chloride solution diluted to 50 ml. The same ferric chloride solution was used throughout a kinetic run. The recorded time of the aliquot is that of complete drainage of the 1-ml. pipet.

The absorbancy (A) reading of the colorimeter is directly proportional to the concentration of the original sodium benzoyl aliphatic hydroxamate. The first-order rate equation then is[20]

$$\log (A - A_\infty) = \frac{-kt}{2.303} + \log (A_0 - A_\infty) \qquad (3)$$

The rate constants were determined from the slope of the graph of log A *vs.* t, $A_\infty = 0$. Good straight lines were obtained; see Fig. 1 for typical examples. All rates were followed to *ca.* 75% complete reaction except for those at 20° (to *ca.* 67% complete reaction) and the determinations of sodium benzoyl acetohydroxamate (to 40–50% complete reaction). The enthalpies and entropies of activation were calculated from rate constants determined at two different temperatures by use of the usual equation.[21]

(20) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," John Wiley and Sons, Inc., New York, N. Y., 1953, p. 28.

(21) Ref. 20, p. 96.

Organic Disulfides and Related Substances. X. Synthesis of 2-Acetamidoethyl Arene- and Alkanethiolsulfonates[1a,b]

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Synthesis of 2-acetamidoethyl thiolsulfonates was studied as typifying alkyl arenethiolsulfonates and alkyl alkanethiolsulfonates, and also because of the possibility that the products would protect against ionizing radiation. Of numerous approaches examined, the most general was by reaction of a sulfonyl iodide and a silver thiolate; preparations were developed for requisite alkanesulfonyl iodides, a class hitherto unknown, and for a representative sodium alkanesulfinate needed as precursor to an iodide. A smooth but less general synthesis involved thioalkylation of sulfinate salts by a thiolsulfonate.

The previous paper of this series reported good protective activity against lethal effects of ionizing radiation for certain thiolsulfonates of structure RSO_2SR' (**1**) in which R and R′ were identical and were aminoethyl or derivatives thereof.[1b] This paper reports syntheses in which R′ is 2-acetamidoethyl. As group R, *p*-tolyl, methyl, and 2-ethylhexyl were chosen to typify the general classes of unsymmetrical alkyl arenethiolsulfonates and alkanethiolsulfonates.

Early syntheses of unsymmetrical thiolsulfonates have been reviewed.[2] Subsequent ones include reaction of a thiol with a sulfonic anhydride[3a] or with a sulfinic acid and ethyl nitrite,[3b] oxidation of an unsymmetrical disulfide[3c,d] or chlorinolysis of two symmetrical disulfides,[3e] and interaction of a disulfide with a sulfinic acid.[3f] All of these methods presently are handicapped, either intrinsically or for want of demonstration of their generality.

The syntheses found best by us thus far are illustrated in Chart I. The reaction of sulfonyl iodides and silver thiolates was our first choice for exploration because it had no obvious limitations except the unavailability of alkanesulfonyl iodides; methanesulfonyl chloride and silver 2-acetamidoethanethiolate (**2**) failed to give an isolable thiolsulfonate.

The reaction of iodides and silver thiolates has been used only with aromatic compounds.[4,5] For synthesis of an alkyl thiolsulfonate, *p*-toluenesulfonyl iodide first was used because it was readily obtainable by reaction of arenesulfinate salts in water with iodine in methanol.[4] With the silver thiolate (**2**) it gave the alkyl arenethiolsulfonate (**3**) in 47% yield. Ether, acetonitrile, benzene, and diglyme gave similar results as solvents; dimethyl sulfoxide reacted. The identity of **3**, and also of **4** and **5** described below, was established by analysis, infrared spectrum, and an acidic reaction on pH test paper upon treatment with *p*-thiocresol.[6]

The alkanesulfonyl iodides needed for synthesis of alkyl alkanethiolsulfonates **4** and **5** apparently represented an unknown class. They could not be obtained by the method used for *p*-toluenesulfonyl iodide; methanesulfonyl iodide was soluble in methanol–water and 2-ethylhexanesulfonyl iodide was hydrolyzed. Attempted conversion of methanesulfonyl chloride by means of sodium iodide failed, perhaps because of reduction.[7] Methanesulfonyl iodide was obtained in good

(1) (a) Reported in part at the Southeastern Regional Meeting of the American Chemical Society, Gatlinburg, Tenn., Nov. 1-3, 1962. This investigation was supported by the U. S. Army Medical Research and Development Command, Department of the Army, under Research Contract No. DA-49-193-MD-2030. Results are abstracted from portions of the Ph.D. dissertation of R. R. C., Vanderbilt University, 1963, and the forthcoming dissertation of T. F. P. (b) Paper IX: L. Field, A. Ferretti, R. R. Crenshaw, and T. C. Owen, *J. Med. Chem.*, **7**, 39 (1964). (c) Du Pont Postgraduate Teaching Assistant, 1962–1963. (d) Texaco Fellow in Chemistry, 1961–1962.

(2) R. Connor, "Organic Chemistry, An Advanced Treatise," Vol. I, H. Gilman, Ed., 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1943, pp. 906–908.

(3) (a) L. Field, *J. Am. Chem. Soc.*, **74**, 394 (1952). This method was used only for symmetrical thiolsulfonates, but should be adaptable to unsymmetrical ones. (b) G. Kresze and W. Kort, *Ber.*, **94**, 2624 (1961). (c) G. Leandri and A. Tundo, *Ann. chim.* (Rome), **44**, 74 (1954); *Chem. Abstr.*, **49**, 4563 (1955). (d) L. Field, H. Härle, T. C. Owen, and A. Ferretti, *J. Org. Chem.*, **29**, in press; (e) I. B. Douglas and B. S. Farah, *ibid.*, **24**, 973 (1959). (f) J. L. Kice and K. W. Bowers, *J. Am. Chem. Soc.*, **84**, 2384 (1962).

(4) D. T. Gibson, C. J. Miller, and S. Smiles, *J. Chem. Soc.*, **127**, 1821 (1925).

(5) R. Child and S. Smiles, *ibid.*, 2696 (1926).

(6) A consequence of the reaction $RSO_2SR' + R''SH \rightarrow RSO_2H + R'SSR''$ (*cf.* D. Barnard and E. R. Cole, *Anal. Chim. Acta*, **20**, 540 (1959), and ref. 1b and 3d).

(7) *Cf.* A. Perret and R. Perrot, *Bull. soc. chim. France*, [5]**1**, 1531 (1934).