As might be expected, the effect of a substituent attached to the carbonyl group (sets 28 and 29) is much greater than that of a substituent attached to the benzene ring. It would appear from our results that the stereochemistry of the Diels–Alder adduct is a function of substituent effects.

The data correlated in our study of orientation in Diels–Alder adducts are of the same type as that examined above in the question of the stereochemistry of the adduct. Equations analogous to 22–27 may be written. Our results show that substituent effects in the substituted ethylenes (set 30A) are important in determining the orientation in Diels–Alder adducts. The effect of a substituent in the 2-substituted anthracenes (set 31) on orientation is much smaller than is the effect in the substituted ethylenes, as might be expected from a comparison of the geometries.

Our results for the enone–ethylene cyclization (set 19) show that substituent effects are somewhat smaller here than those observed for the other reactions studied. Substituent effects seem to be comparable to those observed for *cis*-1,2-disubstituted ethylenes acting as dienophiles.

Steric Effects.—We have noted that large differences in the value of β are observed when we compare the reactions of *trans*-1,2-disubstituted ethylenes with cyclopentadiene (or with 2,3-dimethyl-1,3-butadiene), *trans*-1,2-disubstituted ethylenes with 9,10-dimethylanthracene, 1,1-disubstituted ethylenes with 9,10-dimethylanthracene, and *cis*-1,2-disubstituted ethylenes with cyclopentadiene, 2,3-dimethyl-1,3-butadiene, or 9,10-dimethylanthracene. It would seem that these differences in β are due to steric repulsions in the transition state in all of the reactions of the *cis* compounds, and to some extent in the reactions between the *trans*-12- and the 1,1-disubstituted ethylenes and 9,10-dimethylanthracenes.

In certain of the 9-substituted and 9,10-disubstituted anthracenes steric inhibition of resonance seems likely. It is of interest to calculate the interplanar angle θ made by the plane of the substituent with the plane of the anthracene ring system. The variation of σ_R with θ is given by

$$\sigma_{R,\theta X} = \sigma_{RX} \cos^2 \theta \quad (28)$$

The observed rate constant may be expressed as

$$\log k_{X(obsd)} = \alpha\sigma_{IX} + \beta\sigma_{R,\theta X} + h \quad (29)$$

Solving eq 29 for $\sigma_{R\theta}$; eq 28 for $\cos^2 \theta$, and combining, we obtain the relationship

$$\frac{\log k_{X(obsd)} - \alpha\sigma_{IX} - h}{\beta\sigma_{RX}} = \cos^2 \theta \quad (30)$$

Values of θ calculated for the MeO, Ph, and NO_2 groups are 45, 90, and 90°, respectively. In the case of the latter two values, eq 30 gave negative values of $\cos^2 \theta$, and we have therefore considered θ to be 90°. For 9,10-dimethoxyanthracene, we obtain an average value of 58° for θ for the methoxy groups. The difference between this average value of θ and the value calculated for 9-methoxyanthracene is probably not significant.

We have attempted to calculate an average value of θ for the carbomethoxy groups in dimethyl maleate. No results could be obtained for sets 9B and 13A. Steric inhibition of resonance may be one of the factors involved in the surprisingly low reactivity of dimethyl maleate but in these sets some other factor must also be involved. For set 11B we may calculate an average value of θ of 41°. In this connection it should be noted that *cis*-dibenzoylethylene in sets 9 and 11 appears to be free of steric effects. Examination of models suggests that *cis*-dibenzoylethylene may not be distorted to the same extent as dimethyl maleate, and in fact the former may be essentially free of steric inhibition of resonance.

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Imino Lactones. III. The Cyclization of 4-Bromobutyranilide in Aqueous Solution[1a,b]

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The cyclization of 4-bromobutyranilide in aqueous solution has been investigated at 30° in the range of pH 2–14. The rate of cyclization is independent of pH in the range of pH 2–10 and is directly proportional to hydroxide ion activity at higher pH. Below pH 10, the sole reaction product is the imino lactone II, resulting from nucleophilic displacement by the neutral amide function. Cyclization of the amide anion at pH >10 yields both the imino lactone II and the pyrrolidone III in a ratio 1:9. The latter finding appears to constitute the first example of O^--5 ring closure with 4-substituted butyramides.

Recurrent interest in the nucleophilic properties of the amide function has led to several studies of the cyclization of 4-halo-N-substituted butyramides.[2-4] Fusion with solid potassium hydroxide or cyclization in organic solvents containing alkali bases gave 2-pyrrolidones; fusion in the absence of base or reaction in neutral or weakly basic organic media yielded derivatives of 2-iminotetrahydrofuran. In extension of our studies[5] on the chemistry of the imino lactone II in

(1) (a) This work is taken from a dissertation presented by B. A. C. in partial fulfillment of the requirements for the Ph.D. degree, Yale University, 1966. (b) Financial support by the National Institutes of Health (Grant No. AM-04288) is gratefully acknowledged. (c) Predoctoral fellow of the National Institutes of Health, 1965–1966.

(2) H. W. Heine, P. Love, and J. L. Bove, *J. Am. Chem. Soc.*, **77**, 5420 (1955).

(3) C. J. M. Stirling, *J. Chem. Soc.*, 255 (1960).

(4) H. E. Zaugg, R. J. Michaels, A. D. Schaefer, A. M. Wenthe, and W. H. Washburn, *Tetrahedron*, **22**, 1257 (1966).

(5) (a) G. L. Schmir and B. A. Cunningham, *J. Am. Chem. Soc.*, **87**, 5692 (1965); (b) B. A. Cunningham and G. L. Schmir, *ibid.*, **88**, 551 (1966).

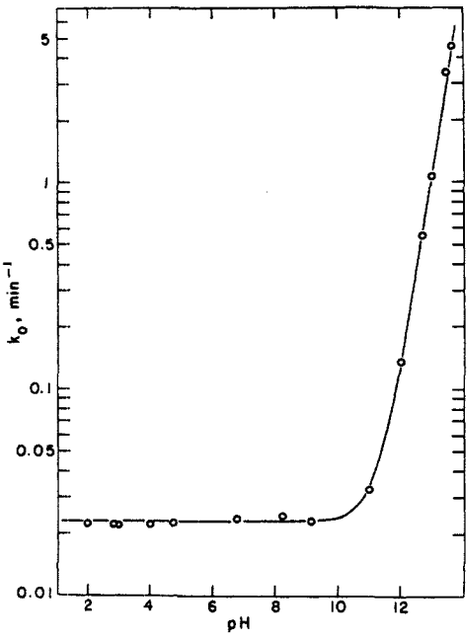


Figure 1.—pH–rate profile for cyclization of 4-bromobutyranilide (I) at 30°. The solid curve is calculated from eq 1, using the constants given in the text.

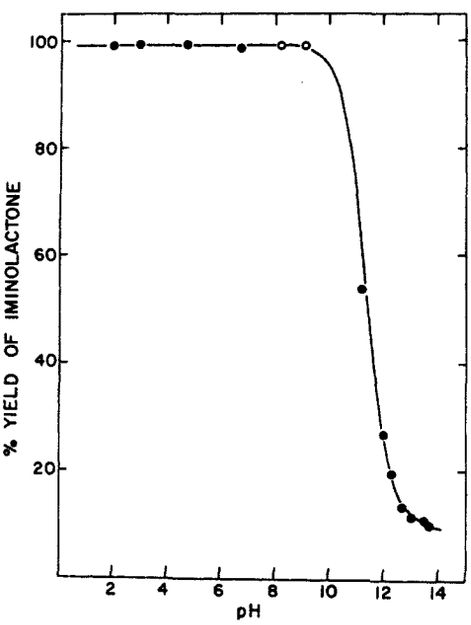


Figure 2.—Effect of pH on the yield of iminolactone produced by cyclization of I: ●, from aniline formation; ○, from absorbance changes (*e.g.*, Figure 3). The solid curve is calculated from eq 3.

aqueous solution, we have investigated the effect of pH on its genesis from 4-bromobutyranilide (I). It was hoped that careful examination of the products of cyclization of the anilide would provide information relevant to the intriguing question of the nucleophilic center of the amide group.

Results

The pH–rate profile for the disappearance of 4-bromobutyranilide in 10% acetonitrile–water (30°) is presented in Figure 1. Increasing the concentration of acetate buffer from 0.01 to 0.1 *M* (pH 4.0 or 4.7) had no effect on the rate. Observed first-order rate constants (k_0) are insensitive to pH below pH 10 and are directly proportional to hydroxide ion activity in more alkaline solution. The curve shown in Figure 1 was calculated from eq 1, with $k_1 = 0.023$ min^{-1} and $k_2' = 10.8\ M^{-1}$ min^{-1}.

$$k_0 = k_1 + k_2'[OH^-] \quad (1)$$

Previous work[5] has shown that the imino lactone II is rapidly and completely converted to aniline (and butyrolactone) at acidic pH. In alkaline solution (pH >8), the much slower hydrolysis of II yields 4-hydroxybutyranilide. These properties of the imino lactone formed the basis of a quantitative determination of the yield of II produced on cyclization of the bromoanilide. For reactions at pH 2–7, all imino lactone formed would be hydrolyzed *in situ* to aniline. Cyclizations at pH >12 were complete before significant conversion of II to hydroxyanilide could occur; after 6 half-lives of reaction, aliquots were acidified to ensure quantitative hydrolysis of any imino lactone present to aniline. Neither the hydroxyanilide nor the pyrrolidone III yield more than 1% aniline under the conditions of cyclization or of aniline assay; the extent of conversion of I to aniline was interpreted, therefore, as a direct measure of the yield of imino lactone II produced on cyclization of the bromobutyranilide. Results are shown in Figure 2 (closed circles). It will be noted that imino lactone was formed in 10% yield in the most alkaline solution examined (0.5 *N* NaOH); under these conditions, the pH-independent reaction (Figure 1) accounts for only 0.5% of the total rate of disappearance of the bromoanilide.

In the region pH 8–9, the transient presence of the imino lactone could be demonstrated kinetically. The spectral changes at 240 mμ resulting from the cyclization of the bromoanilide at pH 9.1 are shown in Figure 3; these data were analyzed by means of consecutive first-order reaction theory, yielding rate constants of 0.023 min^{-1} (for cyclization) and 1.57×10^{-3} min^{-1} (for hydrolysis of the intermediate). The latter value is in excellent agreement with that obtained[5] for the hydrolysis of the imino lactone under the same conditions. The curve of Figure 3 is the result of a calculation based on these rate constants and the assumption that the imino lactone is the sole product of cyclization of the bromoanilide. Similar results were obtained at pH 8.2.

The possibility was considered that the appearance of imino lactone after cyclization in 0.5 *N* NaOH was an experimental artifact. The following experiments were carried out. (a) Solid bromoanilide was added directly to the final reaction mixture, rather than the usual aliquot of a stock solution of bromoanilide in acetonitrile. (b) The acetonitrile stock solution was kept for periods of 1 to 15 min prior to mixing with aqueous alkali. (c) Bromoanilide freshly recrystallized from pentane, benzene–petroleum ether, or ethanol–water was used in simultaneous experiments. In all cases, aniline yields were in the range of 10.0–11.5%, thus ruling out possible imino lactone formation in the neutral environment of the stock solution (*cf.* ref 4) as well as presence of impurities in the starting material.

Direct evidence for the formation of imino lactone after cyclization of the bromoanilide in 0.5 *N* NaOH (30% acetonitrile–water) was obtained by vapor phase chro-

matography. The estimated yield of 7–8% imino lactone was in accord with the aniline yields under the same conditions. In this solvent, neutral cyclization occurs at the same rate as in 10% acetonitrile–water, while the rate of the base-catalyzed reaction is about 30% greater (for equal concentrations of NaOH).

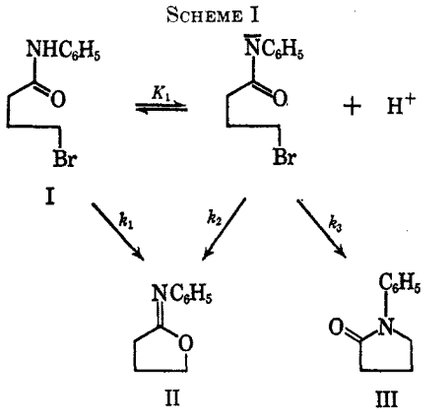
For reactions at pH >12, final optical densities were consistent with the hypothesis that the predominant reaction product was the pyrrolidone III (and not 4-hydroxybutyranilide). Vapor phase chromatography showed the formation of the pyrrolidone in 85% yield (0.5 N NaOH).

Preliminary studies indicated that the neutral cyclization of 4-chlorobutyranilide was about one-twentieth as fast ($k_0 = 1.1 \times 10^{-3}$ min^{-1}) as that of the bromo compound. On a preparative scale, the chloroanilide was converted in 33% yield to 4-hydroxybutyranilide by hydrolysis at 80° in 26% acetonitrile–water, buffered at pH 9. Knobler, *et al.*,[6] have described the same transformation (17% yield) on exposing the chloroanilide to refluxing aqueous sodium carbonate. It is probable that, in both cases, the hydroxyanilide was derived from an intermediate imino lactone.

Discussion

The results of the present study are consistent with the mechanism shown in Scheme I. According to this formulation, cyclization of neutral bromoanilide

SCHEME I



yields exclusively (>99%) the imino lactone II. Cyclization of the amide anion yields both II and III, with the formation of the pyrrolidone occurring nine times more rapidly than that of the imino lactone. The kinetic data presented in Figure 1 exclude the possibility that the imino lactone produced in 10% yield at pH 13.7 arose from a significant contribution of the neutral cyclization process to the sum of the reactions of the bromoanilide.

From the proposed mechanism, it follows readily that the observed first-order rate constant k_0 for bromoanilide disappearance is given by eq 2.[7] The apparent second-

$$k_0 = k_1 + [(k_2 + k_3)K_1/K_w][OH^-] \quad (2)$$

order rate constant k_2' (eq 1) is thus a complex constant; available information does not permit the evaluation of

(6) Y. Knobler, E. Bonni, and T. Sheradsky, *J. Org. Chem.*, **29**, 1229 (1964).

(7) K_w = ion product of water, taken as 10^{-14}.

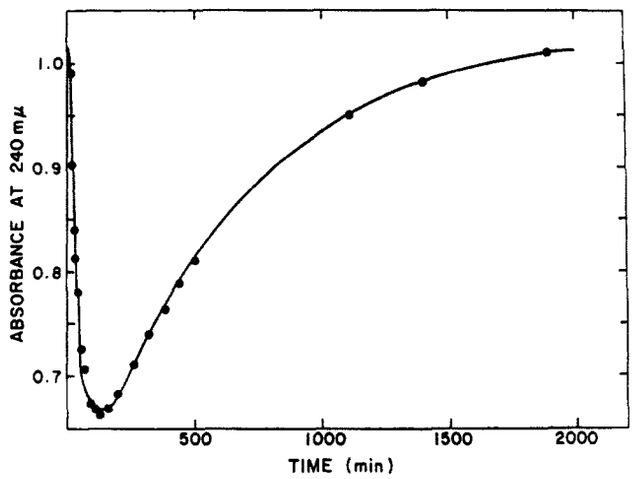


Figure 3.—Absorbance changes during the cyclization of I at pH 9.1. The solid line is the theoretical curve for consecutive first-order reactions, calculated as described in the Experimental Section.

the individual rate or equilibrium constants for the anionic process. The dependence of imino lactone yield on pH is shown in eq 3, where $K' = K_1(k_2 + k_3)/$

$$\% \text{ iminol actone} = \left(\frac{[H^+] + [k_2/(k_2 + k_3)]K'}{[H^+] + K'}\right) 100 \quad (3)$$

k_1; this expression is identical with that describing the titration curve of a univalent acid of apparent $pK_a = pK'$. The curve drawn in Figure 2 is calculated from eq 3 with $pK' = 11.33$ and $k_2/(k_2 + k_3) = 0.097$, the latter value representing the fraction of bromoanilide anion converted to imino lactone. The inflection point of the curve occurs at the pH value where the rates of the neutral and anionic reactions are equal.

Earlier studies[3,4] have shown that neutral cyclization of 4-halobutyramides in organic solvents occurs with 0–5 closure,[8,9] as do the cyclizations of closely related ureido[10] and urethano[10,11] systems. In the presence of alkali bases, N$^-$-5 ring closure has been reported exclusively.[2-4] The present investigation indicates for the first time that O$^-$-5 closure may compete significantly with attack by the nitrogen atom.

The cyclization of N-acyl-2-substituted ethylamines has also received attention. In this case, oxygen attack leads to the formation of a five-membered ring, while nitrogen attack affords three-membered rings. Under neutral conditions, only O-5 closure has been observed, to the exclusion of the competing N-3 process.[12] The base-catalyzed cyclizations, however, give both oxazolines[10,13] (O$^-$-5) and N-acyl aziridines[14] (N$^-$-3).

(8) Closure of a five-membered ring, resulting from nucleophilic attack by an oxygen atom; O-5 and O$^-$-5 refer to attack by neutral and anionic oxygen nucleophiles, respectively. The symbolism is that introduced by Scott, Glick, and Winstein.[10]

(9) Scott, *et al.*,[10] cite the work of Heine[2] as evidence for the existence of N-5 closure in the neutral cyclization of N-phenyl-4-bromobutyramide (see Table II of ref 10). However, although Heine, *et al.*,[2] indeed report the occurrence of a neutral reaction, no evidence is offered concerning the nature of the reaction products.

(10) F. L. Scott, R. E. Glick, and S. Winstein, *Experientia*, **13**, 183 (1957).

(11) F. L. Scott and D. F. Fenton, *Tetrahedron Letters*, 1681 (1964).

(12) (a) S. Winstein and R. Boschan, *J. Am. Chem. Soc.*, **72**, 4669 (1950); (b) H. W. Heine, *ibid.*, **79**, 907 (1957); (c) G. L. Schmir and C. Zioudrou, *Biochemistry*, **2**, 1305 (1963).

(13) (a) H. W. Heine, *J. Am. Chem. Soc.*, **78**, 3708 (1956); (b) C. Zioudrou and G. L. Schmir, *ibid.*, **85**, 3258 (1963).

(14) (a) T. Taguchi and M. Kojima, *ibid.*, **81**, 4316, 4318 (1959); (b) R. D. Guthrie, D. Murphy, D. H. Buss, L. Hough, and A. C. Richardson, *Proc. Chem. Soc.*, 84 (1963).

The factors influencing the choice of reaction pathway have not been delineated.

It has been stated[15] that alkylation of alkali salts of amides generally occurs on the nitrogen atom. Exceptions may be found in the present work and in the O^--5 processes leading to oxazolines (although the latter are probably the consequence of steric inhibition to the N^--3 pathway), as well as in early reports[16] of O-alkylation of carbostyril in the presence of sodium alkoxides. Clearly, the behavior of the amide group as an ambident nucleophile may be subject to varied influences similar to those discovered in more extensively studied systems.[17]

Experimental Section

Materials.—4-Bromobutyranilide[2] (I) had mp 72–73° (lit.[2] mp 75–76°) after recrystallization from pentane, benzene–petroleum ether, or ethanol–water. 1-Phenylpyrrolid-2-one (III) was prepared from I by treatment with ethanolic sodium ethoxide, using a procedure similar to that of Heine, *et al.*,[3] for the corresponding *p*-chloro compound; the product had mp 66–67° (lit.[3] mp 66–68°) after recrystallization from petroleum ether (bp 30–60°). Acetonitrile was treated with calcium hydride and distilled from P_2O_5, according to method D of Coetzee, *et al.*[18] Other chemicals were of reagent grade and were used without further purification.

Kinetic Measurements.—Kinetic studies were carried out at 30°, using as solvent 10% acetonitrile–water (v/v) at ionic strength 0.5, adjusted with added KCl. Constant pH was maintained with chloroacetate, acetate, phosphate, and Tris buffers (at about 0.01–0.04 *M*), or HCl and NaOH in the appropriate ranges.

At values of pH below 6 and above 11, the rate of cyclization of I ($0.7–1.0 \times 10^{-4}$ *M*) was determined spectrophotometrically from the absorbance decrease at 240 mμ. The wavelengths used at intermediate pH follow: pH 6.8, 238 mμ (decrease); pH 8.2 and 9.1, 240 mμ (decrease followed by increase). The equipment employed has been described.[5a] Reactions were initiated by addition of an aliquot of a stock solution of I in acetonitrile to the previously equilibrated buffer solution. The stock solution was generally prepared about 1 min before use.

Several procedures were employed to evaluate first-order rate constants for cyclization, owing to the pronounced effect of pH on the stability of the imino lactone produced. (a) At pH 2–5, the rate of imino lactone hydrolysis is at least 13 times greater than the rate of the cyclization reaction; consequently, the observed absorbance changes reflect the over-all conversion of I to aniline and butyrolactone. The rate constant derived from application of the integrated first-order rate expression is thus that of the rate-limiting cyclization step. (b) At pH 6.8, cyclization occurs about twice as fast as imino lactone hydrolysis. The selected wavelength (238 mμ) represents an (independently determined) isosbestic point for the spectra of the imino lactone and its hydrolysis products. (c) At pH 8.2 and 9.1, the consecutive decrease and increase in absorbance were assumed to represent the successive cyclization of I to II, followed by hydrolysis of II (mainly to 4-hydroxybutyranilide). The rate constants were evaluated by means of consecutive first-order reaction theory, as previously described.[12c,19] The molar extinction coefficients at 240 mμ used in the calculations follow: bromoanilide, 11,900; imino lactone, 6250; hydrolysis products, 11,000. The variation of absorbance at 240 mμ with time (pH 9.1), computed from the theoretical expression, is shown in the curve of Figure 3. (d) At pH 12, the cyclization product is mainly the pyrrolidone (III), accompanied by 10–30% yields of imino lactone. Here, the rate of cyclization is at least 90 times greater than the rate of imino lactone hydrolysis, so that simple first-order analysis could be employed. (e) At pH 11, imino lactone hydrolysis begins to interfere with the accurate determination of a final absorbance value for the cyclization process; the difficulty was circumvented by the use of the Guggenheim method[20] (Δt used was 3 half-lives).

Determination of Products. A. Aniline Assay.—Cyclization of I was allowed to proceed for 8 half-lives (at pH <7) or for 6 half-lives (at pH >11). One-milliliter aliquots of the reaction mixtures were added to 4.5 ml of 2 *M* phosphate buffer (pH 1.7), and the solutions were kept at room temperature for 30 min to achieve complete hydrolysis of the imino lactone. The colorimetric determination of aniline was then performed as previously.[5a] Exposing 4-hydroxybutyranilide to 0.5 *N* NaOH for 6 min and carrying out the aniline assay as above gave <1% aniline. The presence of 30% acetonitrile did not affect the assay method.

B. Imino Lactone II.—To 1.5 ml of acetonitrile was added 33.8 mg of I. As soon as solution was attained (<1 min), 3.5 ml of 0.71 *N* NaOH was added. The reaction mixture was maintained at 30° for 2 min and the acetonitrile was removed by evaporation *in vacuo*. The residual aqueous solution was extracted with five 1-ml portions of ether, centrifugation being used to separate the phases. The combined ether extracts were brought to a total volume of 5 ml and dried over $MgSO_4$. Samples (4 μl) were analyzed by vapor phase chromatography, using columns ($72 \times 1/8$ in.) packed with 20% silicone gum rubber SE-30 on Anakrom ABS (90–100 mesh). Column temperature was 240° and the carrier gas was N_2 (flow rate 27 ml/min).

The fast moving peak corresponded in retention time (3.2 min) to authentic imino lactone. Comparison of peak areas with those obtained from standard solutions indicated a yield of 7–8%, after correction for incomplete recovery (75%) during the extraction procedure. Retention time (*ca.* 4 min) of the much more abundant second component was similar to that of the pyrrolidone III.

4-Hydroxybutyranilide.—4-Chlorobutyranilide[21] (1.0 g, 0.005 mole) was dissolved in a mixture of 30 ml of acetonitrile and 85 ml of 0.2 *M* aqueous Tris buffer, pH 9. The solution was maintained at 75–85° for 3.5 hr and left overnight at room temperature. After reduction *in vacuo* to a volume of 5 ml, the reaction mixture was extracted with five 20-ml portions of ethyl acetate. The combined extracts were dried over $MgSO_4$ and the solvent was removed *in vacuo*. The residual oil was triturated with anhydrous ether; upon chilling an addition of petroleum ether (bp 30–60°), the ethereal extract yielded 0.33 g (37%) of crude product, mp 68–69°. Recrystallization from benzene–petroleum ether gave 0.30 g (33%) of pure 4-hydroxybutyranilide, identical in melting point (78–79°) and infrared spectrum with authentic material.[5a]

(15) (a) N. Kornblum, R. A. Smiley, R. K. Blackwood, and D. C. Iffland, *J. Am. Chem. Soc.*, **77**, 6269 (1955); (b) R. Gompper and O. Christmann, *Ber.*, **92**, 1935 (1959).

(16) (a) P. Friedländer and A. Weinberg, *ibid.*, **18**, 1528 (1885); (b) P. Friedländer and F. Müller, *ibid.*, **20**, 2009 (1887).

(17) For a recent review of the reactions of ambident nucleophiles such as nitrite and phenoxide ions, see R. Gompper, *Angew. Chem. Intern. Ed. Engl.*, **3**, 560 (1964).

(18) J. F. Coetzee, G. P. Cunningham, D. K. McGuire, and G. R. Padmanabhan, *Anal. Chem.*, **34**, 1139 (1962).

(19) See also footnote 37 of ref 5a. The term t_{max} (time of maximum absorbance) in the general treatment should be replaced by t_{min} (time of minimum absorbance) in the present case.

(20) E. A. Guggenheim, *Phil. Mag.*, **2**, 538 (1926).

(21) P. Lipp and F. Caspers, *Ber.*, **58**, 1011 (1925).