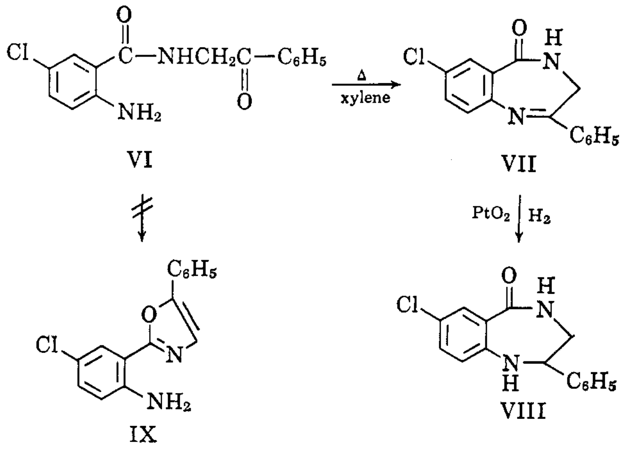
single exchangeable lactam proton is found as a broad singlet at δ 8.70. Since the formation of VIII *via* the lithium aluminum hydride reduction of VII might be considered equivocal, VIII was prepared by the catalytic reduction of VII. The products prepared by both methods of reduction were found to be identical in all respects. Upon deuteration of VIII, the CH_2 multiplet centered at δ 3.59 reverts to a doublet. A CH triplet is centered at δ 4.85 and is unchanged upon deuteration. A broad NH singlet is found at δ 4.33 and a CONH singlet at δ 7.4 both of which vanish on deuteration of the sample.



In a related study it has been found that cyclodehydrochlorination of 3-amino-N-(2-chloroethyl)benzo[*f*]quinoxaline-2-carboxamide afforded 3-amino-2-(2-oxazolin-2-yl)benzo[*f*]quinoxaline instead of 8,9,10,11-tetrahydro-12H-benzo[5,6]quinoxalino[2,3-*e*][1,4]-diazepin-12-one.[8] That the product of reaction is the oxazoline rather than the diazepinone is supported by the fact that the product obtained on diazotization is 3-hydroxy-N-(2-hydroxyethyl)benzo[*f*]quinoxaline-2-carboxamide. Diazotization of 3-amino-N-(2-hydroxyethyl)benzo[*f*]quinoxaline-2-carboxamide also aforded the latter product. Formation of this compound from the diazepinone would be impossible. Since the other members of the series were prepared in the same way, they, too, are undoubtedly oxazolines.

Experimental[9]

7-Chloro-1,2,3,4-tetrahydro-2-phenyl-5H-1,4-benzodiazepin-5-one (**VIII**) *via* **Catalytic Reduction of VII.**—A suspension of 2.7 g. of VII in 50 ml. of absolute ethanol containing 0.15 g. of platinum oxide was allowed to absorb hydrogen in a Parr apparatus for 12.5 hr. The reaction mixture was then heated on a steam bath and filtered. The crystals which were deposited out of solution after cooling the filtrate amounted to 1.5 g., m.p. 166–171°. Recrystallization from ethyl acetate raised the melting point to 172–174°. A mixture melting point with the sample prepared *via* lithium aluminum hydride reduction of VII gave no depression. The infrared spectra were identical.

3-Hydroxy-N-(2-hydroxyethyl)benzo[f]quinoxaline-2-carboxamide. Method A.—Sodium nitrite (1.0 g.) was added in portions to a stirred suspension of 0.5 g. of 3-amino-2-(2-oxazolin-2-yl)benzo[*f*]quinoxaline in 10 ml. of 3 *N* sulfuric acid. After a considerable amount of frothing, an essentially clear solution was obtained. The reaction mixture was then filtered and the filtrate was neutralized with 10% sodium bicarbonate solution. A yellow precipitate was deposited which, after removal by filtration, amounted to 0.4 g., m.p. 284–286°. Recrystallization from aqueous N,N-dimethylformamide raised the melting point to 287–289°; λ_{max} 5.97 (C=O) and 6.51 μ (amide II).

Anal. Calcd. for $C_{15}H_{13}N_3O_3$: C, 63.59; H, 4.63; N, 14.83. Found: C, 63.64; H, 4.47; N, 14.62.

Method B.—Nitrosation of 0.3 g. of 3-amino-N-(2-hydroxyethyl)benzo[*f*]quinoxaline-2-carboxamide with 0.5 g. of sodium nitrite in 10 ml. of 3 *N* sulfuric acid in the manner described above afforded a product which, after recrystallization from aqueous N,N-dimethylformamide, amounted to 0.2 g., m.p. 286–289°. A mixture melting point with the product obtained by method A gave no depression. The infrared spectra were identical.

Acknowledgment.—The authors are grateful to Dr. S. J. Childress for many helpful discussions and suggestions and to Dr. Charles A. Hetzel for his assistance with the n.m.r. spectra.

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[8] A. A. Santilli and T. S. Osdene, *J. Org. Chem.*, **29**, 2066 (1964).

[9] Melting points were taken in capillary tubes (Thomas–Hoover melting point apparatus) and are uncorrected. Infrared spectra were determined in potassium bromide pellets using a Perkin-Elmer Model 21 spectrophotometer. The details of other preparative procedures are given in our previous papers (see ref. 1b and 8).

Coulombic Interaction between *ortho* Substituent and Nucleophile in the Bimolecular Displacement Reaction

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Dispersion forces have long been recognized as a factor affecting equilibria and reaction rates. Bunnett[1] observed that in several bimolecular nucleophilic reaction series nucleophiles of high polarizability were found to be especially reactive, relative to nucleophiles of low polarizability, with substrates having highly polarizable substituents at or near the reaction site. He attributed the enhancement in reaction rate to London forces when the transition state structure is such as to bring highly polarizable groups close to one another. Bunnett and Reinheimer[2] estimated the London force interaction from the reaction rate ratios of *ortho*-substituted benzyl chlorides with methoxide, thiophenoxide, and iodide ions. More recently Reinheimer[3] examined the *o*-CH_3:*p*-CH_3 and *o*-Br:*p*-Br reaction rate ratios of benzyl chlorides with the same nucleophiles. He demonstrated that calculations of the magnitude of London forces operating in the transition state indicated that the differences in rate ratios with MeO^-, $C_6H_5S^-$, and I^-, for a given *ortho* substituent, may be assigned to these forces. However, it was previously pointed out by the author[4] that comparison of the *o*-CH_3:*p*-CH_3 and *o*-Br:*p*-Br rate ratios, with the same reagents, showed trends contrary to those expected from London interactions alone; *i.e.*, charged nucleophiles invariably gave higher *ortho*:*para* rate ratios with the less polarizable methyl group than with the more polarizable bromo group.[5] Our interest in

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[1] J. F. Bunnett, *J. Am. Chem. Soc.*, **79**, 5969 (1957).

[2] J. F. Bunnett and J. D. Reinheimer, *J. Am. Chem. Soc.*, **84**, 3284 (1962).

[3] D. Dalrymple, J. Reinheimer, D. Barnes, and R. Baker, *J. Org. Chem.*, **29**, 2647 (1964).

[4] A. J. Sisti and S. Lowell, *ibid.*, **29**, 1635 (1964).

[5] For a detailed treatment of the data, see ref. 3 and 4.

this apparent anomaly led us to examine the *ortho*:*para* reaction rate ratios of substituted phenacyl chlorides with various nucleophiles.

Table I presents kinetic data for pyridine and iodide with various *ortho*- and *para*-substituted phenacyl chlorides. Conant[6] reported an average k_2 of 22.4 l. mole^{-1} hr.$^{-1}$ for phenacyl chloride with iodide in acetone at 0°. We observed an average k_2 of 16.5 l. mole^{-1} hr.$^{-1}$. We feel our result is the more reliable since Conant reported iodine liberation during the quenching procedure and he concluded that this was the cause of a large error. We observed no such difficulty in any of our runs.

TABLE I

REACTION RATES[a] FOR SUBSTITUTED PHENACYL CHLORIDES

Substituent	Iodide in acetone, k	Pyridine in methanol, $k \times 10^2$
o-CH_3	67.65	1.73
p-CH_3	63.51	2.20
o-Cl	68.08	3.89
p-Cl	267.9	2.67
o-Br	62.73	7.37
p-Br	272.7	3.70
o-I	44.10	4.38
p-I	268.5	3.74

[a] Rate coefficients in liters per mole hour at 20°.

Table II presents the *ortho*:*para* rate ratios for the substituents CH_3, Cl, Br, and I with pyridine and iodide ion. Examination of the *ortho*:*para* rate ratios in Table II indicates that the previously mentioned trend persists in the phenacyl system; *i.e.*, the highly polarizable iodide ion gives significantly higher *ortho*:*para* rate ratios with the less polarizable methyl group than with the more polarizable halogen groups. Acetate in methanol and other charged nucleophiles in methanol show similar trends.[7] A striking and significant feature of the data in Table II is the complete reversal of these trends with the neutral reagent, pyridine, and, in particular, it should be noted that the *o*-halogen:*p*-halogen ratio is higher for pyridine than for iodide. A similar reversal was obtained with diethyl sulfide in methanol.[7]

TABLE II

RATE RATIOS OF SUBSTITUTED PHENACYL CHLORIDES

Reagent	$k_{o\text{-}CH_3} : k_{p\text{-}CH_3}$	$k_{o\text{-}Cl} : k_{p\text{-}Cl}$	$k_{o\text{-}Br} : k_{p\text{-}Br}$	$k_{o\text{-}I} : k_{p\text{-}I}$
I^-	1.06	0.24	0.23	0.17
C_5H_5N	0.79[a]	1.46	1.99	1.17

[a] A value of 0.77 was obtained for the corresponding phenacyl bromides in acetone at 20° by J. W. Baker [*J. Chem. Soc.*, 445 (1938)].

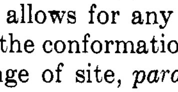
Before considering any favorable or unfavorable interactions between the nucleophile and the *ortho* substituent which may affect the reaction rate one must allow for the substituent's total polar and steric effects upon the reaction rate. The total polar effect of the substituent should be nearly identical from the *ortho* and *para* positions and this effect should cancel in the *ortho*:*para* ratio. This is based upon the assumption of the equivalence of either σ and σ^* or ρ and ρ^*, properties which have been substantiated by Taft.[8] One may argue that the total polar effect of the substituent from the *ortho* and *para* positions does not cancel in the *ortho*:*para* rate ratio, since the *ortho* substituent should exert a greater inductive influence on the reaction rate owing to its proximity to the reaction site. This reasonable possibility can be accounted for as follows. For the bimolecular displacement reaction with phenacyl halides it is known that the reaction rate is retarded by electron-donating groups and enhanced by electron-withdrawing groups (pyridine in acetone[9] at 20°, $\rho = +0.55$; pyridine in methanol[7] at 20°, $\rho = +0.60$; and iodide in acetone[7] at 20°, $\rho = +1.0$). Therefore, if one assumes a difference in the total polar effect of p-halogen $\rightarrow$ o-halogen, the resulting increase in reaction rate for the *o*-halogen isomer, relative to the *p*-halogen isomer, should be greater for iodide than pyridine. It reasonably follows that as a result of this polar difference the *ortho*:*para* rate ratio for iodide should be greater than that for pyridine. This is clearly not the case (Table II). For the o-CH_3:p-CH_3 rate ratio any polar difference should retard the rate of o-CH_3 more than that of p-CH_3. This is not observed for iodide ion (Table II).

Any adverse steric interaction between the phenacyl hydrogens and the *ortho* substituent in the transition state should be more or less constant for any nucleophile. Thus, the *ortho*:*para* ratios for a given substituent with different nucleophiles should allow for this adverse steric effect. Similarly, the *ortho*:*para* ratio for a given substituent allows for any effect upon the reaction rate owing to the conformational difference which accompanies a change of site, *para* → *ortho*, since this difference should be the same for all attacking reagents.

Thus, the differences between the *ortho*:*para* rate ratios for both nucleophiles with a given substituent, to a large extent, appear to reflect interactions resulting from the nucleophile and the *ortho* substituent (steric, London, or others may be significant). Any adverse steric effects between the nucleophile and the *ortho* substituent should be less for the highly polarizable iodide[10] than that for pyridine.

Therefore, from the factors discussed (polar, steric, and conformational) and the arguments presented, the iodide *ortho*:*para* rate ratios should be greater or at least equal to the corresponding ratios for pyridine. The observed results are contrary to this (Table II).

The generally accepted mechanism for the nucleophilic displacement reaction upon α-halo ketones is one which involves neighboring-group orbital overlap.[11] The transition state structure is believed to resemble I, in which the nucleophile, N, is perpendicular to the O–C–C plane. Examination of Dreiding molecular models indicated that for the *o*-halophenacyl chlorides



I

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[6] J. B. Conant and W. R. Kirner, *J. Am. Chem. Soc.*, **46**, 232 (1924).

[7] Unpublished results from this laboratory.

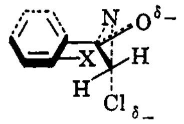
[8] R. E. Taft, "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, pp. 559–659.

[9] H. H. Jaffé, *Chem. Rev.*, **53**, 206 (1953).

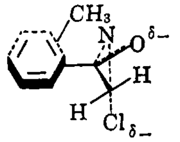
[10] R. G. Pearson and J. O. Edwards, *J. Am. Chem. Soc.*, **84**, 16 (1962).

[11] A. J. Sisti and S. Lowell, *Can. J. Chem.*, **42**, 1896 (1964), and references therein.

a reasonable transition state structure is as depicted in II. The halogen is placed away from the negative field of the carbonyl oxygen therefore, avoiding electrostatic repulsion.[12] For the *o*-methylphenacyl chloride the transition state structure, depicted in III, appears plausible since one avoids unfavorable steric interactions between the methyl group and the phenacyl hydrogen without introducing steric interactions with the carbonyl oxygen.



II



III

Close inspection of these models of the transition state structure make it apparent that nucleophile–*ortho*-substituent interactions are possible. It is therefore suggested that favorable coulombic interactions (ion–dipole) between the nucleophile and *ortho*-substituent are responsible for the observed differences in the *ortho*:*para* rate ratios for iodide and pyridine. Nucleophiles developing a partial positive charge (pyridine, diethyl sulfide, and the like) at the transition state can interact favorably with the negative end of the dipole present in all *o*-halogen substituents, thereby stabilizing this transition state more than that of the *p*-halogen isomer. This favorable interaction with *o*-halogen substituents would obviously be absent with charged nucleophiles which possess a partial negative charge at the transition state (iodide, acetate, thiosulfate, and the like). Similarly, favorable ion–dipole interactions would obtain between the *o*-CH_3 substituent and charged nucleophiles, and be absent with neutral nucleophiles. In the benzyl system we tentatively ascribe part of the differences between *o*-CH_3:*p*-CH_3 and *o*-Br:*p*-Br rate ratios with charged nucleophiles to favorable ion–dipole interactions with the *o*-CH_3 substituent.[13]

Presently, a study of the effect of solvent upon the rate ratios with pyridine is under investigation.

Experimental

2-Chloro-2′-methylacetophenone was prepared according to the procedure of Austin,[14] b.p. 88–89° (0.7 mm.), lit.[14] b.p. 129–130° (11 mm.).

2-Chloro-4′-methylacetophenone was prepared according to the procedure of Korten and Scholl[15] from *p*-methylacetophenone (Eastman Chemical Co.), m.p. 57–58°, (lit.[16] m.p. 57–58°).

2′-Bromo-2-chloroacetophenone was prepared according to the procedure of Korten and Scholl[15] from *o*-bromoacetophenone,[17] b.p. 86–87° (0.3 mm.).

The 2,4-dinitrophenylhydrazone melted at 166–166.5°.

Anal. Calcd. for $C_{14}H_{10}BrClN_4O_4$: C, 40.65; H, 2.41. Found: C, 40.86; H, 2.61.

4′-Bromo-2-chloroacetophenone was prepared according to the procedure of Korten and Scholl[15] from *p*-bromoacetophenone (Aldrich Chemical Co.), m.p. 116–116.5°.

Anal. Calcd. for C_8H_6BrClO: C, 41.20; H, 2.65. Found: C, 41.16; H, 2.53.

2,4′-Dichloroacetophenone was prepared according to the procedure of Korten and Scholl[15] from *p*-chloroacetophenone (Aldrich Chemical Co.), m.p. 101–101.5° (lit.[18] m.p. 101°).

2′,2-Dichloroacetophenone was prepared according to the procedure of Korten and Scholl[15] from *o*-chloroacetophenone,[17] b.p. 86–87° (0.05 mm.).

The 2,4-dinitrophenylhydrazone melted at 170–171°.

Anal. Calcd. for $C_{14}H_{10}Cl_2N_4O_4$: C, 45.54; H, 2.93; N, 15.18. Found: C, 45.58; H, 2.66; N, 15.60.

2-Chloro-2′-iodoacetophenone was prepared according to the procedure of Korten and Scholl[15] from *o*-iodoacetophenone,[17] b.p. 112.5° (5 mm.).

Anal. Calcd. for C_8H_6ClIO: C, 34.25; H, 2.15. Found: C, 34.38; H, 2.05.

2-Chloro-4′-iodoacetophenone was prepared according to the procedure of Korten and Scholl[15] from *p*-iodoacetophenone,[18] m.p. 126–126.5°.

Anal. Calcd. for C_8H_6ClIO: C, 34.25; H, 2.15. Found: C, 34.34; H, 2.17.

The yields of new chlorides were 40–70%.

Reagents.—Acetone (Baker reagent grade) was treated with potassium permanganate under reflux, filtered, and distilled several times from anhydrous calcium oxide. Methanol (Baker reagent grade) was distilled from sodium methoxide. Pyridine (Baker reagent grade) was dried over potassium hydroxide and distilled. Potassium iodide (Baker reagent grade) was dried at 110° and used directly.

Kinetic Procedure.—All liquid halides were distilled several times before use and all solid halides were recrystallized to constant melting point before use. Reaction solutions were prepared at thermostat temperature by standard procedures.

Potassium Iodide.—The reactions were conducted in 15 × 125 mm. test tubes containing thin-walled inner bulbs into which were pipeted acetone solutions of the organic halide. The solution of potassium iodide in acetone was pipeted directly into the test tube. The initial concentrations of phenacyl chlorides for the *o*- and *p*-bromo and -iodo compounds were 0.033 *M*, and, for iodide, 0.011 *M;* for *p*-chloro, 0.028 *M*, and iodide, 0.011 *M;* for *o*-chloro, 0.031 *M*, and iodide, 0.013 *M;* for *o*-methyl, 0.016 *M*, and iodide, 0.021, 0.022, and 0.014 *M* (three runs); and for *p*-methyl, 0.023 *M*, and iodide, 0.015 *M*. The total volume taken was 20 ml. The reactions were started by breaking the inner tube with a glass rod probe inserted through a Teflon stopper. The reaction was quenched by flooding the reaction mixture with 25 ml. of ice water and 10 ml. of ether. The ether layer was extracted twice with water and the water extracts were combined. The aqueous solution was then titrated potentiometrically for iodide ion. A total of six to seven points were obtained at different times all of which agreed to within 5–8%.

Pyridine.—Initial concentrations of pyridine and halide in methanol in all runs were equal (0.06–0.07 *M*). The reactions were followed by changes in ionic conductivity with a Jones bridge.[19]

Products.—An adequate product analysis was conducted by Bordwell[20] for iodide with a series of *para*-substituted phenacyl chlorides in acetone. Phenacyl chloride with iodide in acetone yielded a 65% conversion to phenacyl iodide.[20] Adequate product studies were conducted by Pearson[19] and Baker[21,22] for pyridine in methanol and acetone. Quantitative conversions to the pyridinium salts were reported[22] for phenacyl bromide, *o*-methylphenacyl bromide, and *p*-methylphenacyl bromide. Each of the above studies indicated that a bimolecular displacement reaction was taking place.

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[12] P. D. Bartlett and E. N. Trachtenberg, *J. Am. Chem. Soc.*, **80**, 5808 (1958).

[13] Other favorable coulombic interactions, ion–induced dipole and induced dipole–induced dipole (London), and their relative contributions will be discussed at a later time.

[14] J. Austin, *J. Am. Chem. Soc.*, **54**, 656 (1932).

[15] D. A. Shirley, "Preparation of Organic Intermediates," John Wiley and Sons, Inc., New York, N. Y., 1951, p. 71.

[16] V. Auwers, *Ber.*, **39**, 3761 (1906).

[17] R. Hauser, *Org. Syn.*, **30**, 70 (1950).

[18] R. W. Strassburg, R. A. Gregg, and C. Walling, *J. Am. Chem. Soc.*, **69**, 2141 (1947).

[19] R. G. Pearson, *ibid.*, **74**, 5130 (1952).

[20] F. G. Bordwell and W. J. Brannan, Jr., *ibid.*, **86**, 4645 (1964).

[21] J. W. Baker, *J. Chem. Soc.*, 1128 (1933); 445 (1938); 1148 (1932).

[22] J. W. Baker, *Trans. Faraday Soc.*, **37**, 632 (1941).