

Ultraviolet absorption spectrum of the 2,4-dinitrophenylhydrazone in ethyl alcohol exhibited a maximum at 395 $m\mu$ (ϵ 41,870). Braude and Forbes' record for the 2,4-dinitrophenylhydrazone of 10-methylbicyclo[5:3:0]dec-1(7)-en-8-one λ_{max} 394 $m\mu$ (ϵ 26,000) in chloroform.

Anal. Calcd. for $C_{22}H_{22}N_4O_4$: C, 65.01; H, 5.46; N, 13.79. Found: C, 65.36; H, 5.65; N, 13.55.

(7) E. A. Braude and W. F. Forbes, *J. Chem. Soc.*, 2208 (1953).

The aqueous alkaline solution from the above experiment was acidified with dilute hydrochloric acid and extracted with ether. Evaporation of the ether gave 0.6 g. (28%) of an acid which crystallized from dilute ethyl alcohol in colorless needles, m.p. 162°, undepressed by an authentic sample of α -cycloheptenyl- β -phenylsuccinic acid (II) obtained above.

ABBASSIA, CAIRO, EGYPT

[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

5,7-Dinitro-3-coumaranone and the Mechanism of the Bimolecular Nucleophilic Displacement Reaction in Phenacyl Compounds^{1a}

BY PAUL D. BARTLETT AND EDWARD N. TRACHTENBERG^{1b}

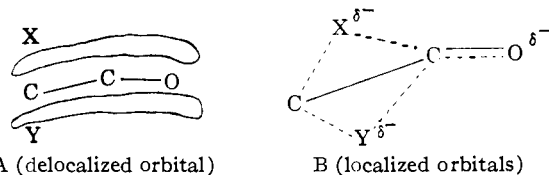
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5,7-Dinitro-3-coumaranone (I) has been synthesized as a model phenacyl pseudo-halide free of steric hindrance to displacement of the dinitrophenoxide group but requiring any attacking reagent to enter the molecule in the plane of the 5-membered ring and of the carbonyl group. In reaction with potassium iodide in acetone, I shows $\Delta H^\ddagger = 31.3 \pm 1.9$ kcal., $\Delta S^\ddagger = 25.4 \pm 6.0$ cal./degree. For comparison ω -(4-aceto-2,6-dinitro)-phenoxyacetophenone (II) has $\Delta H^\ddagger = 10.2 \pm 1.2$ kcal. and $\Delta S^\ddagger = -30.0 \pm 4.4$ cal./degree. These results indicate a stereochemical requirement for the special reactivity of phenacyl halides; mechanisms in which such a requirement is implicit are discussed.

It has long been known that α -haloketones show remarkably enhanced reactivity in bimolecular nucleophilic displacement (S_N2) reactions. For this behavior, which is also displayed to a lesser degree in α -halo nitriles, amides, esters and carboxylate anions, explanations of several different kinds have been offered. The suggestion has been made² that inductive electron withdrawal by the carbonyl group activates the adjacent saturated carbon toward nucleophilic displacement. Pearson and co-workers³ proposed that the proximity of the positively charged carbon atom of the carbonyl group electrostatically facilitates approach of the displacing reagent along its normal path to the adjacent carbon atom. At the other extreme, covalent bond formation of the reagent with the carbonyl carbon atom has been viewed as a possibility,⁴ to be followed by intramolecular rearrangement and displacement. In a variant of this mechanism of covalent participation, the possibility of epoxide formation in a follow-up step was considered; strong arguments have been brought against both of these schemes.³ Finally, two mechanisms based upon orbital overlap without complete covalent bonding to carbonyl carbon have been proposed by Dewar⁵ and by Winstein⁶; in both cases the approach of the reagent is regarded as facilitated, not by electrostatic or inductive effects, but by partial overlap, respectively, with the π -molecular orbital of the C—C—O system or with the p-orbital of the carbonyl carbon.

There is evidence to indicate that inductive electron withdrawal from a carbon atom does not in general increase, but may rather decrease, the ease of a displacement reaction at that carbon atom. This can be seen in alkyl halides substituted at the β -position by halogen⁷ or alkoxy.⁸ A less clear case is the unreactivity of α -halosulfones,^{9,10} or of chloroacetylmesitylene,¹¹ where steric factors cannot be ruled out.

The mechanisms of Dewar and of Winstein have a stereochemical implication which has suggested the experiments of this paper. In both, the atoms C—C=O of the phenacyl side chain determine a plane, and the entering and departing groups in the displacement reaction must occupy positions above and below that plane in order to find the orbitals of the two adjacent carbon atoms with which they are to interact.



Any structural feature of a phenacyl halide or pseudo-halide which would prevent the YCCX plane from being perpendicular to the CCO plane in a transition state for displacement should sharply raise the energy of that transition state if A or B is a correct picture of the reaction. It is not possible to put such constraints on a halogen atom; however, the fact that a 2,4- or 2,6-dinitrophenoxy group can be displaced as an anion makes possible the construction of I, whose reactivity in comparison with II should provide the desired test.

(1) (a) Presented at the 14th International Congress of Pure and Applied Chemistry, Zurich, 1955. (b) Standard Oil (Indiana) Fellow, 1951-1952.

(2) E. D. Hughes, *Quart. Revs.*, **5**, 245 (1951).

(3) R. G. Pearson, S. H. Langer, F. V. Williams and W. J. McGuire, *THIS JOURNAL*, **74**, 5130 (1952).

(4) J. W. Baker, *Trans. Faraday Soc.*, **37**, 632 (1941).

(5) M. J. S. Dewar, "The Electronic Theory of Organic Chemistry," Clarendon Press, Oxford, 1949, p. 73.

(6) Suggested by S. Winstein at the International Colloquium on Molecular Rearrangements and Walden Inversion at Montpellier, France, 1950; see S. Winstein, E. Grunwald and H. W. Jones, *THIS JOURNAL*, **73**, 2700 (1951), footnote 16.

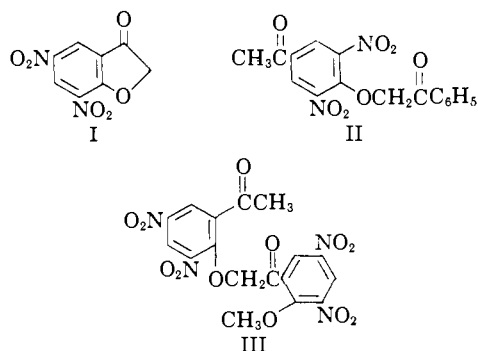
(7) J. Hine and W. H. Brader, Jr., *ibid.*, **75**, 3964 (1953).

(8) F. B. Tutwiler and R. L. McKee, *ibid.*, **76**, 6342 (1954).

(9) T. B. Johnson and I. B. Douglass, *ibid.*, **63**, 1571 (1941).

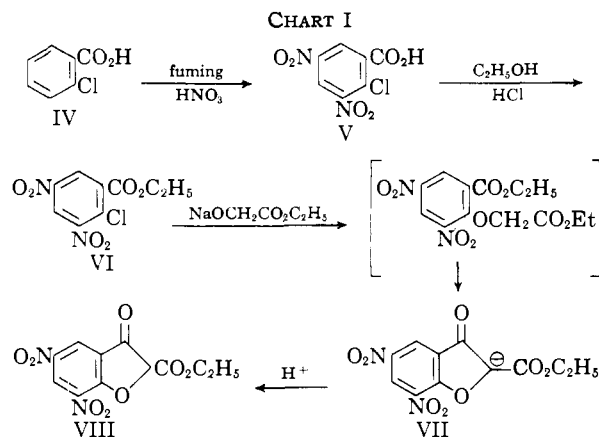
(10) F. G. Bordwell and G. D. Cooper, *ibid.*, **73**, 5184 (1951).

(11) S. H. Babcock, P. I. Nakamura and R. C. Fuson, *ibid.*, **54**, 4407 (1932).



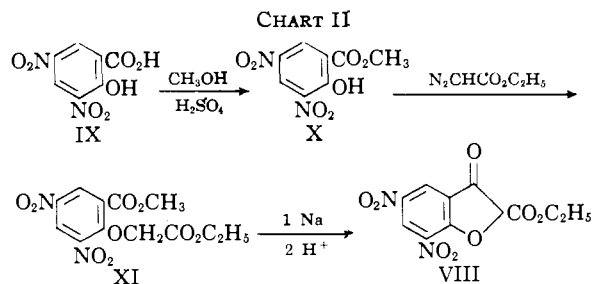
Although III is an excellent analog of I on electronic grounds, it was abandoned in favor of II for several reasons. First, the presence of the methoxyl in III creates a second site for nucleophilic attack which, although presumably much less reactive than the phenacyl site, is nevertheless undesirable. Second, the presence of the *o*-methoxyl introduces conventional steric hindrance to displacement not present in the analog I. Third, the removal of the substituents from the benzoyl part of the molecule simplifies the synthetic task and, at the same time, introduces only a small error in rate. This error, furthermore, is in such a direction as to make any observed enhanced reactivity in II over I a minimum.¹² The inversion of the positions of the acetyl and nitro groups in II was necessitated by synthetic difficulties but should introduce no significant change in reactivity.

In the synthesis of 5,7-dinitro-3-coumaranone (5,7-dinitrobenzo-3-furanone), direct nitration of 3-coumaranone proved infeasible because of the sensitivity of this molecule to oxidation, and many of the methods which are applicable to the synthesis of the unsubstituted compound proved of little value here. Two successful methods involving the intermediate, ethyl 5,7-dinitro-3-coumaranone-2-carboxylate, are outlined in Charts I and II.



Compound II, ω -(4-aceto-2,6-dinitro)-phenoxyacetophenone, was readily synthesized from 3,5-dinitro-4-hydroxyacetophenone, available from the

(12) Baker, ref. 4, has found that a *p*-nitro group enhances rate by a factor of 2.56 and *p*-methoxy lowers rate by a factor of 0.74 in phenacyl halides. Since the *m*-nitro group should be less effective than the *p*-nitro and the *o*-methoxyl might be expected to be less retarding than the *p*-methoxyl, the net effect of introducing these groups probably would be to enhance rate by a factor of about four.



nitration of *p*-hydroxyacetophenone. Attempted displacement of phenacyl bromide with the corresponding phenolate anion of the dinitrated compound led to total recovery of the latter even after refluxing for a week in ethyl acetate. This shows the marked lack of nucleophilic activity of this species in which the negative charge is apparently well distributed over the nitro and aceto groups. Taking advantage of the corollary property, the acidity of the phenolic hydroxyl, we found that this molecule condensed readily with ω -diazoacetophenone to yield the desired II.

In order to compare the reactivity of I and II, the rate of displacement with iodide ion in dry acetone was studied. This reaction, which can be followed by titrating unreacted iodide, offers several decided advantages over other conceivable choices. It is clearly of the second order, is not attended by side reactions which might be expected with a more basic nucleophilic reagent, and leads to attack exclusively at the α -carbon. The phenyl-oxygen link in both the proposed substrates is very much like a picryl ether bond; it might be subject to attack by other agents, but is apparently inert to iodide ion.¹³

Experimental¹⁴

Ethyl 5,7-Dinitro-3-coumaranone-2-carboxylate (Chart I).—Eastman Kodak Co. *o*-chlorobenzoic acid was dinitrated according to the method of Ullman¹⁵ and the product esterified by the Cohn¹⁶ modification of the Fischer esterification to yield ethyl 2-chloro-3,5-dinitrobenzoate (VI). In a 500-ml. 3-neck flask fitted with a Hershberg stirrer, condenser and dropping funnel was placed 150 ml. of absolute ether, 2.29 g. (0.022 mole) of ethyl glycolate and 0.53 g. (0.022 mole) of sodium hydride. After stirring for about 3–5 hours, the gray color of the hydride was replaced by the white color of the suspension of the desired sodium salt, and to this was added 3 g. (0.011 mole) of VI in 50 ml. of absolute ether. After refluxing six hours, the solution, which had turned yellow on the addition of the ethyl 2-chloro-3,5-dinitrobenzoate, had darkened to a deep brown color. After cooling, the mixture was cautiously hydrolyzed with ice-water, the aqueous layer separated and acidified with dilute sulfuric acid to precipitate 0.6 g. of a brown solid, m.p. 220–223°. After numerous recrystallizations alternately from ethanol-water and ethyl acetate-cyclohexane mixtures, there was obtained in very small yield a batch of light tan needles, m.p. 227–229°. This β -ketoester gave a purple color with alcoholic ferric chloride solution.

Anal. Calcd. for C₁₁H₉O₈N₂: C, 44.57; H, 2.72; N, 9.46. Found: C, 44.66; H, 2.72; N, 9.36.

Ethyl 5,7-Dinitro-3-coumaranone-2-carboxylate (Chart II).—The above synthesis left much to be desired as to yield and ease of isolation of the product and was therefore supplanted by the following procedure. Eastman Kodak Co.

(13) J. B. Conant and W. R. Kirner, *THIS JOURNAL*, **46**, 232 (1924).

(14) All melting points are corrected. The microanalyses were performed by Dr. S. M. Nagy and his associates at the Massachusetts Institute of Technology.

(15) F. Ullman and G. Engi, *Ann.*, **366**, 82 (1909).

(16) P. Cohn, *Monatsh.*, **22**, 385 (1901).

3,5-dinitrosalicylic acid (100 g., 0.438 mole) was refluxed for three hours with 500 ml. of absolute methanol containing 50 ml. of concentrated sulfuric acid. During the later stages of the reaction, ester precipitated as beautiful pale yellow needles, and a crop of 63 g. was filtered after cooling the reaction mixture. Concentration of the filtrate yielded a second and third crop which were added to the first and recrystallized from methyl acetate-methanol to yield 104 g. (98%) of pure methyl 3,5-dinitrosalicylate, m.p. 129–130°. To a solution of 121 g. (0.50 mole) of methyl 3,5-dinitrosalicylate in 700 ml. of ethyl acetate was added a few drops of concentrated sulfuric acid and then 61 g. (0.535 mole) of ethyl diazoacetate. After refluxing for 20 hours, the solvent was removed by distillation and the residual oil recrystallized from either carbon tetrachloride or ethanol (with charcoal clarification) to yield 143 g. (87%) of ethyl (2-carbomethoxy-3,5-dinitro)-phenoxyacetate (XI) as light yellow needles, m.p. 91.5–92.5°. This diester (16.4 g., 0.05 mole) was dissolved in 700 ml. of absolute ether containing just enough dioxane (purified by the method of Fieser¹⁷) to effect solution. To this solution stirred with a Hershberg stirrer and at reflux in an atmosphere of dry nitrogen were added two drops of absolute ethanol and 1.15 g. (0.05 mole) of sodium sand prepared by melting sodium in xylene, shaking vigorously, cooling and washing several times with dry ether. After stirring and refluxing for 36 hours, the dark brown mixture was cooled and cautiously poured into 400 ml. of ice-water. (Extreme caution must be exercised at this point since on several occasions the sodium, having become coated with salt, failed to react completely and then ignited the organic solvent on the addition to ice-water). The ether layer was separated and concentrated to an oil which was taken up in hot ethanol and then cooled to return 60–70% of starting diester. From the aqueous layer on acidification with dilute sulfuric acid, filtration of the resultant precipitate and recrystallization of the latter from ethanol-water was isolated 2.2 g. (15% conversion, 43% yield) of ethyl 5,7-dinitro-3-coumaranone-2-carboxylate (VIII) as light tan needles, m.p. 227–229°. This product proved to be identical with that obtained in the previously described procedure on the basis of melting point, mixed melting point and infrared spectrum.

5,7-Dinitro-3-coumaranone.—A solution of 1 g. (0.0034 mole) of the ketoester VIII in 100 ml. of 50% acetic acid-hydrochloric acid containing a catalytic amount of zinc chloride was refluxed for 12 hours, filtered hot and cooled to precipitate 5,7-dinitro-3-coumaranone (I). After filtration and recrystallization from acetic acid-water, there was obtained 0.6 g. (80%) of light tan needles, m.p. 183–184°; infrared spectrum in chloroform: peaks at 5.72(s), 6.08(s), 6.19(m), 6.41(s), 6.78(m), 6.96(w), 7.11(w), 7.41(s), 7.57(m), 9.14(m), 9.39(m), 10.10(m), 10.66(w), 10.96(w).

Anal. Calcd. for $C_{12}H_8O_6N_2$: C, 42.90; H, 1.80; N, 12.5. Found: C, 42.52; H, 1.95; N, 11.9.

ω -(4-Aceto-2,6-dinitro)-phenoxyacetophenone (II).—To 200 g. of fuming nitric acid cooled to -25° to -30° was added in small portions 27 g. (0.2 mole) of Matheson technical grade *p*-hydroxyacetophenone. The temperature was held in this range both during the hour required for the addition and for an additional hour. The resulting dark brown solution was poured into 1500 g. of ice-water to precipitate a light tan product which on recrystallization from ethanol-ethyl acetate yielded 26.3 g. (72%) of needles, m.p. 133–134°. This product proved to be the known 3-nitro-4-hydroxyacetophenone despite the fact that *o*-hydroxyacetophenone dinitrates under the same conditions. To nitrate the material further, 9.0 g. (0.05 mole) was added in small portions to 150 ml. of sulfuric acid cooled to $5-10^\circ$. With efficient cooling of the solution, 10 g. of potassium nitrate was cautiously added in small portions and the resulting solution further stirred for 6 hours at the same low temperature. The solution was then poured into 500 g. of ice-water and the product which precipitated filtered, washed several times with water and then recrystallized from ethanol to give 7.2 g. (64%) of light yellow needles, m.p. 123.2–123.5°. If the reaction is run at a slightly higher temperature, the major product is picric acid.

Anal. Calcd. for $C_8H_6O_8N_2$: C, 42.50; H, 2.66; N, 12.5. Found: C, 42.70; H, 2.81; N, 12.4.

(17) L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., Boston, Mass., 1941, p. 368.

To a vigorously stirred solution of 3,5-dinitro-4-hydroxyacetophenone (4.52 g., 0.02 mole) in 100 ml. of ethyl acetate to which had been added two drops of concentrated sulfuric acid was added dropwise a solution of 3.0 g. (0.0205 mole) of ω -diazoacetophenone (prepared by the method of Newman¹⁸) in 50 ml. of ethyl acetate. The solution was refluxed overnight, concentrated and the resulting oil recrystallized from ethanol and then from benzene to yield 4.7 g. (68%) of light yellow needles, m.p. 143.0–143.5° (II).

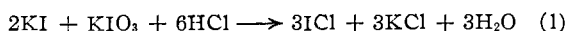
Anal. Calcd. for $C_{16}H_{12}O_7N_2$: C, 55.81; H, 3.51; N, 8.14. Found: C, 56.04; H, 3.63; N, 8.07.

Kinetic Measurements. Reagents.—Reagent grade Merck chloroform, du Pont hydrochloric acid, Merck potassium iodide and Mallinckrodt potassium iodate were employed. The latter two salts were dried for four hours and stored in a desiccator. Merck reagent grade acetone was further purified by refluxing one liter with 15 g. of potassium permanganate until the color disappeared (*ca.* 3 hours), filtering the precipitated manganese dioxide, drying the filtrate over phosphorus pentoxide and then distilling it from the latter. Just prior to use, it was redistilled from phosphorus pentoxide through a 20-cm. Widmer column and the fraction boiling at $56.4-56.6^\circ$ collected.

Thermal Control.—For the measurements at 0° , a slush of finely crushed ice and water kept well stirred in a wide-mouth Dewar was found to maintain the temperature at $0 \pm 0.001^\circ$. For the runs at 10.02° , a water-bath in a wide-mouth Dewar was used. It was stirred vigorously and controlled within $\pm 0.03^\circ$ by suitable adjustment of the contact area of a large and a small cold finger with the bath. For the higher temperatures, an oil-bath heated by a 40 watt bulb and regulated by a mercury-toluene thermoregulator served to maintain the temperature to $\pm 0.01^\circ$.

Procedure.—The reactions were run in sealed tubes containing inner bulbs open at one end. The procedure used, which is a slight modification of the Conant and Kirner method,¹⁹ was to blow a thin-walled bulb in one end of a 6 mm. glass tube about 9 cm. in length. This tube was provided with a lip to prevent creeping and then inserted into a 15×125 mm. test-tube which had previously been indented in the bottom and which bore a file scratch about 6 cm. from the top. The tube was then constricted quite close to the top, the inner bulb filled with 1 ml. of a standard solution of organic substrate in absolute acetone delivered from an automatic pipet, the outer tube similarly filled with a standard solution of potassium iodide in absolute acetone, the tube cooled in a freezing mixture of Dry Ice in 60% carbon tetrachloride-40% chloroform and sealed at the constriction. The tubes, which were protected from atmospheric moisture during all of the above operations, were then placed in a vertical position in the constant temperature bath and permitted to come to thermal equilibrium (about one hour). At an appropriate time, a tube was removed from the bath, shaken vigorously so as to break the inner bulb, and then immediately reinserted in the bath. For the reactions at the lower two temperatures, the reaction was stopped by removing the tube and applying a glass rod, previously brought to red heat, to the scratch mark on the tube. The vessel, so cracked, was dropped into a quenching solution of 5 ml. of chloroform, 5 ml. of concentrated hydrochloric acid and 20 g. of ice contained in a 250-ml. glass-stoppered bottle and shaken vigorously. For the higher temperatures, the reaction was quenched by cooling to -80° quickly and then proceeding as above.

The two layers which formed in the glass-stoppered bottle were allowed to settle, the chloroform layer containing all the organic matter was removed with a fine-tipped medicine dropper and 5 ml. of fresh chloroform and 20 g. more of ice added. It was found in test experiments that such removal of chloroform did not affect the titer of iodide. The unreacted iodide was then titrated by the Andrews method.¹⁹ This titration is sensitive to acid concentration, and optimum conditions had to be determined in all cases by titrating known quantities of iodide. Thus, in the later points of the kinetic runs, it was found necessary to employ lesser amounts of hydrochloric acid. It was also found desirable to work rapidly and to keep the solutions cold during the titration. The equation for the Andrews titration is



(18) M. S. Newman and P. Beal, *THIS JOURNAL*, **71**, 1506 (1949).

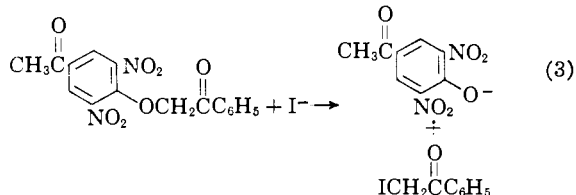
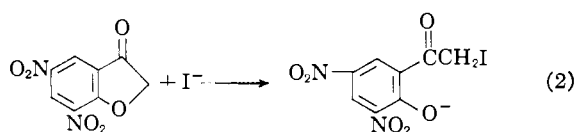
(19) L. W. Andrews, *ibid.*, **25**, 756 (1903).

If one uses too low an acid concentration or permits the solutions to warm up, the iodine chloride is hydrolyzed. Too high an acid concentration results in indistinct endpoints which come far before the equivalence point. With too high an acid concentration large amounts of iodine are also produced, presumably from hydrogen iodide reduction of the product, phenacyl iodide. Conant,¹³ who used higher acid concentrations than those used in this work, frequently encountered this latter difficulty. In most of the runs no iodine was produced in the quenching operation or during the run. In two of the runs iodine was produced but in insignificant amounts, as determined by thiosulfate titration.

All runs were done in duplicate at each temperature using different ratios of iodide to organic substrate. The rate constants were determined from a plot of the usual second-order equation, the best fit to the data, as well as the standard deviations, being determined by the method of least squares. The reactions generally were followed through two half-lives with an average of seven points being used to determine each rate constant. The potassium iodide concentrations were in the range of $3-4 \times 10^{-3}$ molar and the organic substrates in the range of 0.003 to 0.018 molar. Blanks were run in all cases to check the initial iodide titer, and these were found to agree with the amounts determined by weight to within two parts per thousand.

Results and Discussion

The kinetic results for reactions 2 and 3 are listed in Table I.



The values of the enthalpy of activation ΔH^\ddagger and the entropy of activation ΔS^\ddagger are in Table II.

TABLE I

Compound	T, °C.	k × 10 ³ , l./mole sec.
ω-(4-Aceto-2,6-dinitro)- phenoxyacetophenone (II)	0	11.00 ± 0.28
5,7-Dinitro-3-	10.02	22.17 ± 1.21
coumaranone (I)	49.38	1.57 ± 0.10
	58.95	6.60 ± 0.15

TABLE II

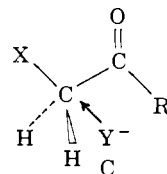
Compound	ΔH^\ddagger	ΔS^\ddagger
ω-(4-Aceto-2,6-dinitro)- phenoxyacetophenone	10.2 ± 1.2	-30.0 ± 4.4
5,7-Dinitro-3-coumaranone	31.3 ± 1.9	25.4 ± 6.0

These results correspond to a difference in reactivity of almost 9000-fold at 0° but equal rate constants at 103°. The large difference of over 20 kcal. in ΔH^\ddagger means that an enormous activation present in II is absent in I. This disparity in energy barrier to reaction in the two compounds is not fully manifest in the rates of reaction because of a very large entropy difference which tends to offset it. An entropy difference in this direction might be expected for two reasons. First, the type of transition state being formed in the reaction of I is that to be expected of an SN2 reaction unassisted by phenacyl activation; *i.e.*, bond breaking leads or at least keeps pace with bond formation; one anion is losing its solvation while another one is

becoming solvated. The charge at the transition state is highly dispersed relative to that in the starting materials, and the solvation may be becoming less tight. The transition state for II, involving phenacyl activation, derives its favorable energy according to formula A or B from accommodation of charge on the small keto oxygen and this may involve extra orientation of solvent molecules; it surely involves a lead of bond formation over bond breaking. Some part of the entropy differential undoubtedly comes from the fact that in I a ring is being opened, while at the transition state from II, a highly oriented structure equivalent to a small ring is being formed.

The representations of the transition state according to A and to B are both consistent with the geometrical evidence here developed. They differ, however, in appearance. Dewar's transition state has the entering and departing groups sharing a pair of electrons each in a molecular π -orbital embracing the carbonyl group and the carbon atom where the displacement is occurring; nothing is said concerning the detailed locations of these groups. The idea behind B is that the entering group may be following a path of least repulsion in a region of common overlap between the carbonyl and α -carbon atoms, and this suggests a location forming an approximately isosceles triangle between these centers. Considerations of microscopic reversibility require, at least in the displacement of halogen by halogen, that the departing group shall also follow such a path. Representation B involves the use of *p*-orbitals in the phenacyl derivative; since it is from such orbitals that the molecular π -orbitals of A are formed, it may be argued that there is no essential difference between A and B. The latter scheme shares with resonance representations generally the property of indicating charge distributions more clearly than the molecular orbital picture. It is an important point here that, in contrast to allylic systems, bond formation leads over bond breaking and there is negative charge upon the phenacyl structure in the transition state.

The lack of typical phenacyl activation in I is also consistent with the electrostatic hypothesis mentioned earlier.³ That mechanism, however, imposes a less specific geometrical requirement upon the transition state. Barring steric hindrance, the *electrostatically* most favored path for an approaching reagent would be according to C, with



all solid bonds being in the plane of the paper. The obvious steric hindrance from R would, by this mechanism, force a compromise to be attained by a limited rotation about the C-C bond, in no case reaching the 180° point corresponding to the structure of I. A final decision between electrostatic and orbital-overlap mechanisms is not afforded by the present evidence. It may be noted, however,

