perature before adding dry ether and filtering off the solid. The ether solution was washed with cold, dilute hydrochloric acid and aqueous sodium bicarbonate, then was dried over sodium sulfate, and distilled. A 73% yield of allyl 2-allyloxyethyl carbonate was collected at 124–125° (18 mm.). The molar refractivity was 47.69 as compared to a calculated value of 47.77. A sample without inhibitor did not undergo polymerization over a period of five months.

5-Allyloxy-1-chloro-2-pentene (?).—To a mixture of 80 cc. of cold carbon disulfide, 27 g. of 1,3-butadiene and 1.5 g. of anhydrous zinc chloride was slowly added 42.5 g. of allyl chloromethyl ether with thorough chilling and stirring. After a resting period of 15 hours at 5–15° the product was poured into ice. The organic layer was removed, dried, and a trace of pyrogallol was added. Distillation yielded 21 g. (33%) of a constant boiling fraction: b.p. 90–92% (25 mm.). The molecular refractivity (44.65) conforms with that calculated (44.72) for $C_8H_{13}ClO$.

The halogen in this compound reacted in aqueous alcohol solution with aqueous silver nitrate. Silver chloride precipitated instantly.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

Mechanism of the Reaction of α-Haloketones with Weakly Basic Nucleophilic Reagents

BY RALPH G. PEARSON, STANLEY H. LANGER, FORREST V. WILLIAMS AND WILLIAM J. McGUIRE

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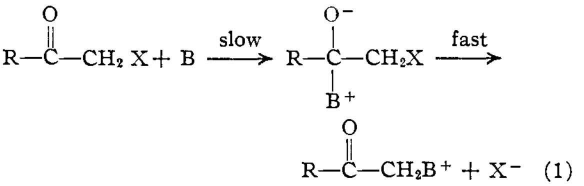
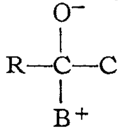
The second-order rate constants for the reactions of pyridine and thiourea with a number of organic bromides, including several in which the bromine is alpha to a carbonyl group, have been determined. It is found that the haloketones and haloesters are relatively more reactive toward the weakly basic but easily polarized thiourea than are the other halides. This is interpreted as meaning that the activating influence of the carbonyl group is largely electrostatic in nature. Arguments are presented against an epoxide intermediate in the reaction of haloketones with weakly basic nucleophilic reagents and against a rate determining addition of the reagent to the carbonyl group.

The well known reactivity of α-haloketones and α-haloesters toward nucleophilic reagents has been the subject of several discussions. Hughes[1] and Ingold have ascribed the reactivity to a polar effect in which the electron-attracting carbonyl group induces a positive charge on the carbon atom holding the halogen. This then facilitates the bringing up of a reagent with a negative center to a position where it can push out the halogen by the usual back-side displacement process. Baker[2] has postulated a mechanism involving addition of the basic reagent to the carbonyl group in a rate determining step, followed by a rapid intramolecular displacement

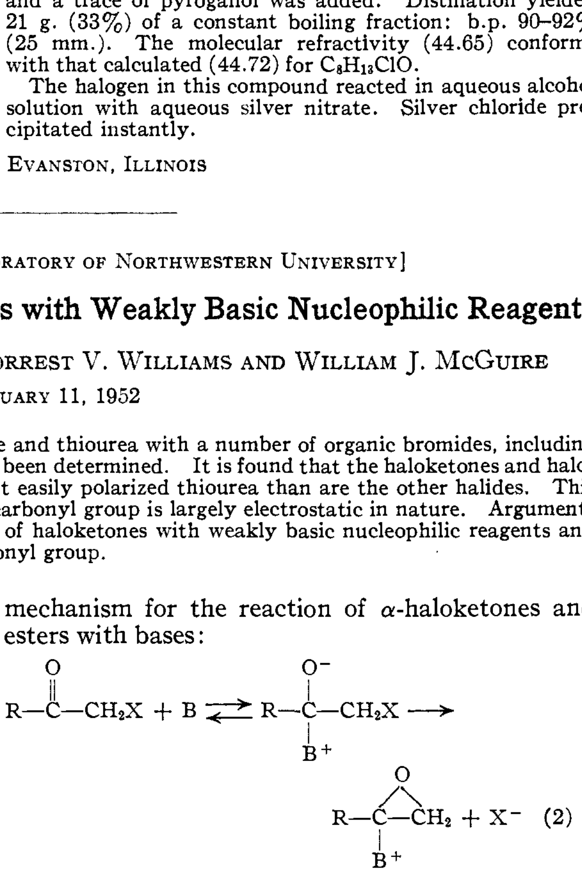


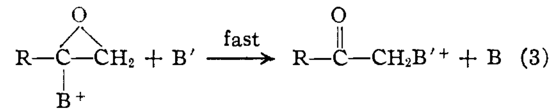
$$R-\overset{\overset{O}{\|}}{C}-CH_2\,X+B \xrightarrow{\text{slow}} R-\underset{\underset{B^+}{|}}{\overset{\overset{O^-}{|}}{C}}-CH_2X \xrightarrow{\text{fast}} R-\overset{\overset{O}{\|}}{C}-CH_2B^+ + X^- \quad (1)$$

Winstein, Grunwald and Jones[3] have mentioned the possibility of contributions from structures such as $R-\underset{\underset{B^+}{|}}{\overset{\overset{O^-}{|}}{C}}-CH_2X$ in the transition state for the displacement of X by B in haloketones.



The recent isolation of a moderately stable epoxide[4] in the reaction of an α-haloketone with sodium methoxide and the evidence that the epoxide is an intermediate in the formation of other products of the reaction[5] leads to another possible mechanism for the reaction of α-haloketones and esters with bases:





If some stage of reaction (2) is slow then this mechanism can agree with the second-order kinetics which have always been found for reactions of α-haloketones, etc., with nucleophilic reagents.[6] A key point in this mechanism is that the reagent B′ need not be the same as the reagent B.

In criticism of Hughes and Ingold's explanation it can be mentioned that substitution of an electron-attracting group in a halide frequently *deactivates* toward nucleophilic displacement reactions. Thus α-halosulfones and α-halonitroparaffins are quite unreactive. Also as Hinshelwood, Laidler and Timm[7] have pointed out, for a neutral reagent one might well predict that a negative substituent would deactivate by causing the negative halogen to be held more tightly.

Baker's mechanism can be ruled out as a general one by the observation that phenacyl bromide is 54 times as reactive as phenacyl chloride toward pyridine in ethanol at 55.6°.[8] This is inconsistent

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[1] E. D. Hughes, *Trans. Faraday Soc.*, **37**, 603 (1941).

[2] J. W. Baker, *ibid.*, **37**, 643 (1941).

[3] S. Winstein, E. Grunwald and H. W. Jones, THIS JOURNAL, **73**, 2700 (1951).

[4] (a) Temnikova and Kropacheva, *J. Gen. Chem. U.S.S.R.*, **19**, 1917 (1949); (b) C. L. Stevens, W. Malik and R. Pratt, THIS JOURNAL, **72**, 4758 (1950).

[5] Reference 4 and A. M. Ward, *J. Chem. Soc.*, 1541 (1929).

[6] (a) J. W. Baker, *ibid.*, 1148 (1932); 1128 (1933); (b) H. T. Clark, *ibid.*, **97**, 416 (1910); (c) J. B. Conant and W. R. Kirner, THIS JOURNAL, **46**, 232 (1924).

[7] C. N. Hinshelwood, K. J. Laidler and E. W. Timm, *J. Chem. Soc.*, 848 (1938).

[8] Reference 6 (b); also we have observed that phenacyl bromide reacts 126 times as fast as phenacyl chloride with thiourea in methanol at 35°.

with a rate-determining step involving addition to the carbonyl group but is consistent with a rate step involving displacement of the halogen where bromine is always more reactive than chlorine.

To investigate the possibility that coördination of the nucleophilic reagent B with the carbonyl plays a major part in the displacement process, the rate constants for the reactions of a number of bromides with pyridine and thiourea in methanol were measured and are here presented. This pair of reagents was selected because pyridine is a stronger base than thiourea by a factor of 10^5, but thiourea is a better nucleophilic reagent than pyridine presumably because of the greater polarizability of the sulfur atom.[9] It is assumed that the strength of binding to the carbonyl group will be more a function of base strength than of nucleophilic character.

To examine the possibility that an epoxide intermediate is common to all normal substitution reactions of α-haloketones or esters with bases, the relative rates of pyridine and aniline with phenacyl bromide were found and compared to the relative amounts of the reaction products obtained in a competition reaction. If an epoxide intermediate is formed in the rate-determining step, equation (2), and if the final product is obtained in a separate fast step, equation (3), then no correlation between the rates and the product composition need exist. If, on the other hand, the final product is formed in the rate step, then the ratio of products should be predictable from the ratio of rate constants.[10]

Experimental

Materials.—Commercially available C.P. organic bromides and thiourea were redistilled or recrystallized before use. 2,4,6-Trimethylphenacyl bromide was made according to the literature[11] and recrystallized from ether–alcohol, m.p. 54° (lit. 55–56°). Medicinal grade pyridine was distilled over potassium hydroxide. Methanol was dried with magnesium turnings. Aniline was distilled from zinc dust.

Methods.—Rates of reaction were determined in anhydrous methanol at 35° in all cases and at 0° in a few cases. The reactions were followed by the conductance change as bromide ion was liberated. The apparatus and general methods have been described.[12] The ratio of base to bromide was one to one for the reactive bromides and ten or twenty to one for the less reactive ones. Excellent second-order kinetics were obtained in the first case and the first-order constants obtained in the second case were divided by the initial concentration of base to get the second-order constants. To check the error involved in this procedure a number of runs were made with phenacyl bromide and thiourea using varying amounts of the base. For the less reactive bromides with pyridine it was inconvenient to wait until the reaction was complete to obtain the equilibrium resistance. Accordingly the pyridinium salts were made by standard methods and synthetic mixtures of the correct composition prepared to measure the equilibrium resistance. The data collected are shown in Tables I and II.

There is a complication in that for phenacyl bromide, *p*-bromophenacyl bromide and ethyl bromacetate, cyclic compounds are formed from the isothiuronium salts by splitting out of water. Thus phenacyl bromide with thiourea yields 2-amino-4-phenylthiazolinium bromide.[13] 2,4,6-Trimethylphenacyl bromide forms an isothiuronium salt which does not cyclize to a thiazole because of steric hindrance at the carbonyl group.[14]

TABLE I

SECOND-ORDER RATE CONSTANTS FOR ORGANIC BROMIDES WITH PYRIDINE AND THIOUREA

Methanol Solvent at 35°

No.	Bromide	k, Pyridine[a] l./mole-min.	k, Thiourea[a] l./mole-min.
1	Ethylene bromohydrin	1.7×10^{-5}	4.8×10^{-4}
2	*β*-Phenoxyethyl bromide	2.0×10^{-5}	5.3×10^{-4}
3	*n*-Propyl bromide	1.0×10^{-4}	2.8×10^{-3}
4	Ethyl bromide	2.3×10^{-4}	4.3×10^{-3}
7	2,4,6-Trimethylphenacyl bromide	2.5×10^{-4}	4.0×10^{-2}
5	Allyl bromide	8.3×10^{-3}	3.3×10^{-1}
6	Benzyl bromide	3.1×10^{-2}	8.5×10^{-1}
8	Ethylbromacetate	8.5×10^{-3}	1.8
9	Phenacyl bromide	4.5×10^{-2}	29.9
10	*p*-Bromophenacyl bromide	7.2×10^{-2}	46.2

[a] Duplicate runs were made in each reaction studied.

TABLE II

EFFECT OF CONCENTRATION AND ADDED SUBSTANCES ON RATE OF REACTION OF PHENACYL BROMIDE AND THIOUREA

Methanol Solvent at 0°

Phenacyl bromide, moles/liter	Thiourea, moles/liter	Ratio	k, l./mole-min.
0.0209	0.0209	1	2.59
.1502	.0074	2	2.23
.0087	.0264	3	2.16
.0123	.181	15	1.95
.0085	.153	18	1.93
.0050	.151	30	1.80
.0052	.183	35	1.84
.0035	.135	40	1.72
.0250	.0250	1	2.55[a]
.0426	.0426	1	2.73[b]
.0534	.0534	1	2.56[c]

[a] Containing 1 *M* water. [b] Containing 0.007 *M* potassium bromide. [c] Containing 0.025 *M* *p*-toluenesulfonic acid.

Competition experiments between excess aniline and pyridine for a limited amount of phenacyl bromide were carried out by using 1 *M* aniline and pyridine and 0.05 *M* bromide. Analysis of the completely reacted mixture was carried out by diluting with water (150 ml. to 50 ml. of reaction mixture) and extracting excess aniline, excess pyridine and phenacylaniline with ether. The aqueous solution was then acidic due to the presence of anilinium and pyridinium hydrobromide equivalent to the amount of phenacylaniline formed. This was titrated with 0.1 *N* base using a potentiometric method for the end-point. Excess base was then added and a sufficient time allowed to cleave the phenacylpyridinium

TABLE III

COMPETITION REACTION BETWEEN 1 *M* PYRIDINE AND 1 *M* ANILINE FOR 0.05 *M* PHENACYL BROMIDE

Methanol at 35°

1 *M* pyridine only $k = 4.45 \times 10^{-2}$

1 *M* aniline only $k = 7.24 \times 10^{-2}$

1 *M* aniline + 1 *M* pyridine $k = 11.9 \times 10^{-2}$

analysis gives 0.0308 *M* phenacylaniline and
0.0208 *M* phenacylpyridinium bromide

ratio of rates = 1.62 ratio of products = 1.48

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(9) The well known nucleophilic reactivity of iodide ion, carbanions, bisulfide ions and the like, seems best explained on the basis of easily distorted electrons which can form an incipient covalent bond without bringing the rest of the molecule close enough to cause excessive repulsion.

(10) Bateman, Hughes and Ingold, *J. Chem. Soc.*, 1187 (1937).

(11) W. Jacobs and M. Heidelberger, *J. Biol. Chem.*, **21**, 455 (1915).

(12) R. G. Pearson, THIS JOURNAL, **69**, 3100 (1947); **71**, 2220 (1949).

(13) A. Hantzch and V. Traumann, *Ber.*, **21**, 938 (1888).

(14) L. C. King and R. J. Hlavacek, THIS JOURNAL, **72** 3722 (1950).

bromide.[15] The solution was back-titrated with acid and the change in titer gave the amount of pyridine quaternary salt formed. The methods were checked with known samples. The data are shown in Table III.

Discussion

Figure 1 shows the result of plotting log k_{pyr} against log k_{thio} for ten bromides whose rate constants differ over a range of 10^5 toward thiourea and 10^4 toward pyridine. It is evident that there is a good correlation for the six non-carbonyl bromides. The slope is unity showing that the ratio k_{thio}/k_{pyr} remains constant. The three bromoketones and the bromoester correlate roughly with each other but differ from the other halides in being markedly more reactive toward thiourea. Also the ratio k_{thio}/k_{pyr} increases with the reactivity of the halide. In view of the large polarizability of thiourea (high sensitivity to electrical effects) these results are interpreted as evidence that the activating influence of the carbonyl group is largely electrostatic in nature.[16,17]

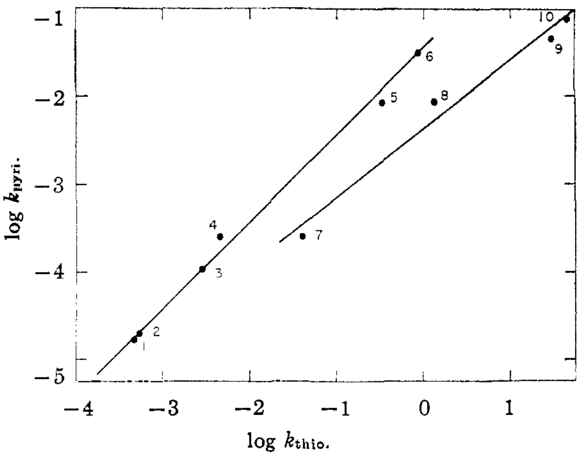

Fig. 1.—Log rate constant for pyridine reaction *versus* log rate constant for thiourea reaction. Compounds numbered as in Table I.

In view of the polyfunctional nature of thiourea and the type of products obtained from three of the keto halides, the possibility exists that addition of the NH_2 group to the carbonyl takes place prior to the displacement of halogen. There is one strong argument, at least, against such a mechanism; the weak basicity of thiourea makes it almost inevitable that acid catalysis would be required for such an addition. However the measured rate is seen in Table I to be insensitive to added strong acid.

The results of the competition experiment between excess pyridine and aniline for a limited amount of phenacyl bromide are in agreement with a displacement reaction leading directly to the products. Thus the rates are seen to be additive (Table III) and the ratio of the products is the same as the ratio of the rate constants within experimental error. The results render improbable a mechanism involving epoxide formation as in equations (2) and (3) since it would be required that the relative rates for ring opening, equation (3), be the same as for ring closing, equation (2).

In conclusion, the polar effect of the carbonyl group is an activating one compared to sulfone and nitro groups because of the low steric requirements of the carbonyl group. Thus there is easy access to the back side of the α-carbon atom in a region near the positive end of the carbonyl dipole, while in sulfones and nitro compounds this position is blocked off by negatively charged oxygen atoms.[18] Also in 2,4,6-trimethylphenacyl bromide where the carbonyl group is hindered, the reactivity is reduced because the favored direction of approach is blocked.

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(15) R. G. Pearson and R. L. Dillon, THIS JOURNAL, **70**, 1933 (1948).

(16) Conant, *et al.* (ref. 6c and J. B. Conant and R. E. Hussey, *ibid.*, **47**, 476 (1925); J. B. Conant, R. E. Hussey and Kirner, *ibid.*, **47**, 488 (1925)) have measured the rates of six of the chlorides corresponding to the bromides of Fig. 1 with iodide ion. If log k_I is plotted instead of log k_{thio}, a plot almost identical with Fig. 1 is obtained. Thus iodide ion and thiourea are similar reagents.

(17) It is worth mentioning the relative reactivities toward iodide ion of the series $C_6H_5CO(CH_2)_nCl$.[16] These are 105,000:87:230 for n = 1,2 and 3 (n-butyl chloride is unity on this scale). The great drop in going from $n = 1$ to $n = 2$ compared to the small increase in going from $n = 2$ to $n = 3$ may be indicative of other than electrostatic forces acting since these would be expected to diminish steadily with increasing n. The situation is not very clear however since the series $CH_3COO(CH_2)_nCl$ shows almost exactly the same sequence of reactivities as the chloroketones mentioned above.[16] In the esters the chlorine atom is never alpha to the carbonyl.

(18) F. G. Bordwell and G. D. Cooper, THIS JOURNAL, **73**, 5184 (1951).