Oxidation of Hydrolyzed Polymethyl α-Bromoacrylate, DL-Dimethyltartaric Acid[16] and α-Hydroxyisobutyric Acid.—Approximately 1 meq. of each substance (molecular weight divided by number of carboxyl or carbomethoxy groups in the molecule) was dissolved in 10.0 ml. of 1.5% sodium hydroxide, 100.0 ml. of 0.5% periodic acid solution was added, and the flask was allowed to stand at room temperature. At intervals, one-tenth aliquots were removed, added to excess potassium iodide solution and the iodine quickly titrated with 0.0990 *N* thiosulfate. The results are given in Table I.

Oxidation and Alkaline Cleavage of Saponified Polymethyl α-Bromoacrylate Polylactone.—The polylactone and the product of silver oxide hydrolysis of polymethyl α-bromoacrylate were resistant to degradation by nitric acid, and gave no identifiable products upon treatment with lead tetraacetate or periodic acid. However, the alkaline oxidation methods tried, using permanganate, periodate or hydrogen peroxide, invariably gave some acetone and acetic acid. The best yields of identifiable degradation products were obtained by the procedure below.

Two grams of polymethyl α-bromoacrylate polylactone was weighed into a flask and dissolved in the minimum amount of 5% sodium hydroxide at room temperature. The yellow solution was saturated with carbon dioxide, 30 ml. of 30% hydrogen peroxide was added, and the mixture was warmed gently until the color was discharged and gas evolution began. After one-half hour, 25 ml. of 20% sodium hydroxide was added, and the solution was steam distilled slowly into a chilled receiver containing a saturated solution of 2,4-dinitrophenylhydrazine in 2 *N* hydrochloric acid. Acetone codistilled with the steam over the course of several hours, during which time five additional 10-ml. portions of hydrogen peroxide and 20 ml. more of 20% sodium hydroxide were added. The precipitate in the receiver was collected on a weighed filter paper and dried to constant weight, yielding 369 mg. of acetone 2,4-dinitrophenylhydrazone, m.p. 122–123° crude, 124–125° recrystallized. The compound did not depress the melting point of an authentic sample of acetone 2,4-dinitrophenylhydrazone.

Anal. Calcd. for $C_9H_{10}N_4O_4$: C, 45.39; H, 4.23; N, 23.53. Found: C, 45.17; H, 4.20; N, 23.59.

The residual liquid in the distilling flask was acidified to congo red with 6 *N* sulfuric acid, resulting in vigorous evolution of carbon dioxide, and then distilled until only a sludge of crystals and sirup remained. The total acid content of the distillate was found by titration of an aliquot to be 6.7 meq. The silver nitrate test indicated only a trace of halide. The formic acid content as determined by the mercuric chloride method[17] on an aliquot was 0.74 meq.; consequently the distillate contained 6.0 meq. of acetic acid which was characterized as its *p*-bromophenacyl ester, observed m.p. 84–85°, and *p*-nitrobenzyl ester, observed m.p. 77°. Neither of these derivatives depressed the melting points of authentic samples.

Exhaustive ether extraction of the residual material in the distilling flask and evaporation of the ether yielded a gummy mixture of water-soluble acids which was subjected to partition chromatography by the method of Marvel and Rands,[9] using 0.4 *N* sulfuric acid on 100-mesh silicic acid as the fixed phase and chloroform–butanol mixtures of increasing polarity as the eluant. The "chromatogram" (plot of volume of standard alkali needed to titrate each portion of effluent against total volume of effluent) revealed peaks at the characteristic peak effluent volumes of acetic, itaconic (and/or citraconic), aconitic and citric acids. The presence of citric and aconitic acids was substantiated by characteristic color reactions on the residues obtained by evaporating the proper eluant portions. A chromatograph on a tenfold scale yielded sufficient aconitic acid for positive identification. Aconitic acid crystallized from the eluant, upon concentration, as the free acid, m.p. 175–180° crude (with decomposition), and was characterized by comparison of the infrared spectrum with that of an authentic sample. The presence of either itaconic or citraconic acid or both was indicated by color tests as in the case of citric acid, but the amount isolated from the eluate was too small to permit more definite identification. A trace of acid was eluted from the chromatograph at the peak effluent volume of succinic acid, but evaporation of the eluate portion at this effluent volume yielded only a gum which gave color reactions typical of itaconic or citraconic acid and from which no succinic acid could be isolated.

The yields and relative amounts of the ether-extracted acids varied from run to run, the total yield being increased at the expense of the acetone by decreasing the amount of hydrogen peroxide employed. The maximum amount of these acids obtained was 3.0 meq. from 2.00 g. of polylactone.

(16) R. Fittig, C. Daimler and H. Keller, *Ann.*, **249**, 208 (1888).

(17) Berl-Lunge, "Chem. techn. Untersuchungsmethoden," Vol. V, 8th Ed., Julius Springer, Berlin, 1934, p. 1454.

URBANA, ILLINOIS

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF NORTHWESTERN UNIVERSITY]

Rate of Reaction of Phenacyl Halides with 4-Picoline in Benzene Solution

BY DONALD L. BREBNER AND L. CARROLL KING

RECEIVED SEPTEMBER 22, 1952

The quaternization reaction between phenacyl halides and 4-picoline in benzene solution has been found to obey the rate equation: $d[ArCOCH_2NC_6H_7^+Br^-]/dT = k_2[C_6H_7N][ArCOCH_2Br] + k_3[C_6H_7N][ArCOCH_2Br]^2$. The rate constants for the above equation have been evaluated to allow comparison between observed rates of reaction and the reaction coördinate calculated from the rate constants. The activation energy and entropy of activation for the two rate processes have been evaluated.

The work of Baker[1] has shown that the quaternization reaction of phenacyl halides with pyridine exhibits second-order kinetics in solvents of high polarity such as acetone, 90% acetone–water and 90% ethanol–water. The formation of quaternary salts from alkyl halides and pyridine is a second-order reaction in solvents of all degrees of polarity, unless complicated by reverse reaction or heterogeneity.[2]

In the course of an investigation into the energetics of the reaction of phenacyl bromides with pyridine and its homologs, in non-polar solvents, it was observed that the reaction exhibited large deviation from second-order kinetics. This paper deals with the rationalization of the kinetic results obtained from the reaction of *m*-nitrophenacyl bromide, *p*-phenylphenacyl bromide and 2,4,6-trimethylphenacyl bromide with 4-picoline in benzene solution.

Experimental

Materials.—Reagent-grade thiophene-free benzene was distilled from sodium. Acetone was dried over calcium

(1) J. W. Baker, *Trans. Faraday Soc.*, **37**, 643 (1941).

(2) (a) N. J. T. Pickles and C. N. Hinshelwood, *J. Chem. Soc.*, 1353 (1936); (b) K. J. Laidler, *ibid.*, 1786 (1938); (c) J. A. Hawkins, *ibid.*, **121**, 1170 (1922); (d) C. G. Swain and R. W. Eddy, THIS JOURNAL, **70**, 2989 (1948).

chloride, filtered, dried again over Drierite, and distilled. Reagent-grade pyridine was dried over barium oxide and distilled.

4-Picoline, obtained from the Reilly Tar and Chemical Company, was dried over barium oxide and distilled, the middle third being collected. This process was repeated to give the material used in the rate studies. The purity of the 4-picoline was checked by conversion of a sample in benzene solution to *p*-phenylphenacyl-4-picolinium bromide, which melted at 259–261°, with decomposition. After recrystallization from water containing a trace of HBr, the salt melted at 260–261°, with decomposition. The only likely contaminant, the corresponding salt derived from 3-picoline, melted at 210°.

Eastman Kodak Co. *p*-phenylphenacyl bromide was recrystallized four times from ethyl acetate–Skellysolve C, using Norit "A" to decolorize the solutions; m.p. 128°. *m*-Nitrophenacyl bromide was prepared by the bromination of *m*-nitroacetophenone in chloroform solution at 5°. After four recrystallizations from ethyl acetate–Skellysolve C, the product melted at 96°; reported m.p.[3] 96°. The 2,4,6-trimethylphenacyl bromide was prepared from bromoacetyl bromide and mesitylene using the Friedel–Crafts reaction. After two recrystallizations from ethyl acetate–Skellysolve C, it melted at 58°. Baker[4] reported a melting point of 57°.

Reaction Products. *p*-Phenylphenacyl-4-picolinium Bromide.—This compound was recrystallized from methyl ethyl ketone–methanol containing a trace of HBr; m.p. 260–261°. *Anal.* Calcd. for $C_{20}H_{18}ONBr$: C, 65.21; H, 4.93. Found: C, 64.66; H, 5.12.

2,4,6-Trimethylphenacyl-4-picolinium Bromide.—This compound was recrystallized from methyl ethyl ketone–methanol containing a trace of HBr; m.p. 227°. *Anal.* Calcd. for $C_{17}H_{20}ONBr$: C, 61.08; H, 6.03. Found: C, 60.96; H, 6.16.

***m*-Nitrophenacyl-4-picolinium Bromide.**—This compound was recrystallized from water containing a trace of HBr; m.p. 257–259°. *Anal.* Calcd. for $C_{14}H_{13}O_3N_2Br$: C, 49.87; H, 3.89. Found: C, 49.94; H, 4.00.

Procedure.—The same procedure was used for all kinetic runs. Standard solutions of the reactants were prepared at double the concentration at which they were to be used. The solutions were prepared at the operating temperature, and thermostated one-half hour before use. Twenty-five cc. of the solution of the phenacyl halide was placed in a glass-stoppered flask, and an equal quantity of the solution of the base added from a pipet. The beginning of the addition of the second solution was considered as zero time.

The course of the reaction was followed by weighing the precipitated quaternary salt. The reaction mixture was filtered through a tared sintered-glass funnel containing a wad of glass wool in the barrel to speed the filtration. Five 10-cc. portions of benzene were used to rinse the reaction flask to assure quantitative transfer of the salt to the funnel. The funnels containing the precipitation were dried one hour in a vacuum oven at 50°, cooled to room temperature, and weighed. The beginning of the filtration was taken as the end of the reaction time.

Direct determinations of the solubilities of the salts showed that no solubility correction was necessary when benzene was used as a solvent; solubility losses of 3–5 mg. were observed with the benzene–acetone solvent.

Results and Discussion

Some typical kinetic results are shown in Table I, where k'_2 and k'_3 represent rate constants calculated from the second and third order rate expressions, respectively.

The tendency of the second-order constant to decrease, and the third-order constant to increase as the reaction proceeds, is a general characteristic of all the systems studied in this series of experiments, regardless of the concentrations or ratios of concentrations of the reactants. Experiments with the reaction of *p*-phenylphenacyl bromide with pyridine in benzene solution indicated that the reaction

TABLE I

m-NITROPHENACYL BROMIDE AND 4-PICOLINE, BENZENE SOLUTION, 25.95 + 0.05°, 0.100 *M* REACTANTS

Time, minutes	$a - x$	$10^4k'_2$, l./mole-sec.	$10^3k'_3$, l.²/mole²-sec.
24	0.0906	7.20	7.60
62	.0797	6.83	7.72
120	.0677	6.63	8.20
218	.0547	6.33	8.95
432	.0397	5.85	10.3
1160	.0221	5.07	12.0

was exactly first order in pyridine, but of an order slightly higher than one in the halide.

An interpretation consistent with these results is that the reaction proceeds *via* a combination of two processes, one exhibiting second-order kinetics, and the other, third order. The rate expression

$$dx/dt = k_2(a - x)(b - x) + k_3(a - x)(b - x)^2 \quad (A)$$

x = "concentration" of product at time "t"
a = original concentration of base
b = original concentration of halide

was integrated for the two possible cases $a = b$, $a \neq b$.[5]

When $a = b$, the integral is

$$2.303\, k_3/k_2^2 \log_{10} \frac{(k_2 + k_3a)}{(k_2 + k_3(a - x))} - 2.303\, k_3/k_2^2 \log_{10} \frac{a}{a - x} + \frac{x}{k_2(a(a - x))} = t \quad (B)$$

When $a \neq b$, the integral is

$$\frac{2.303}{k_3(b - a)^2 + k_2(b - a)} \log_{10} \frac{a}{a - x} - \frac{2.303}{k_2(b - a)} \log_{10} \frac{b}{b - x} + \frac{2.303\, k_3}{k_2k_3(b - a) + k_2^2} \log_{10} \frac{k_2 + k_3b}{k_2 + k_3(b - x)} = t \quad (C)$$

In order to obtain values of k_2 and k_3, plots of percentage reaction *vs.* time were made for the reactions studied, values of dx/dt determined at 30% reaction for two runs with different initial concentrations, and the two equations in two unknowns thus obtained solved for k_2 and k_3. The values of k_2 and k_3 were then substituted in either equation (B) or (C) and these equations solved for t, using a succession of values for the concentrations. These results were plotted on the same coördinates as the observed values of percentage reactions *vs.* time. The plots thus obtained are shown in Figs. 1–7. The values of the rate constants in benzene solution are shown in Table II.

TABLE II

Phenacyl bromide	Base	Temp., °C.	10^2k_2, l./mole-min.	$10k_3$, l.²/mole²-min.
p-Phenyl-	4-Picoline	25.95	0.860	0.200
m-Nitro-	4-Picoline	25.95	2.82	1.16
m-Nitro-	4-Picoline	35.35	5.31	2.62

The mixed order rate equation (A) is successful in rationalizing the kinetics of the reaction between phenacyl halides and tertiary bases in benzene solution. However, this does not imply a unique mechanism. It is possible that the observed decrease in the second-order rate constant is caused

(3) J. W. Baker, *J. Chem. Soc.*, 1154 (1932).
(4) J. W. Baker, *ibid.*, 445 (1938).
(5) For a somewhat different treatment of this integral, see P. D. Bartlett and R. W. Nebel, THIS JOURNAL, **62**, 1345 (1940).

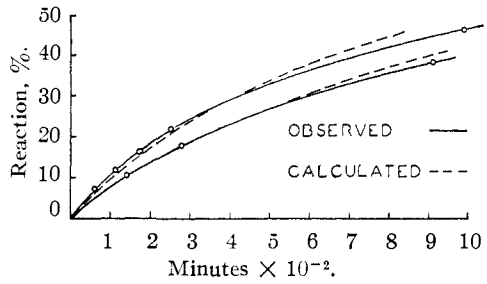


Fig. 1.—*p*-Phenylphenacyl bromide and 4-picoline, 25.95°: upper lines, 0.100 *M* reactants; lower lines, 0.0750 *M* reactants.

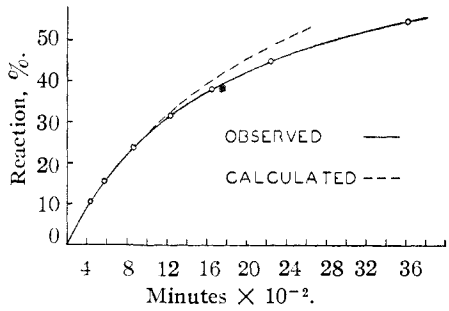


Fig. 2.—*p*-Phenylphenacyl bromide and 4-picoline, 25.95°, 0.0500 *M* reactants.

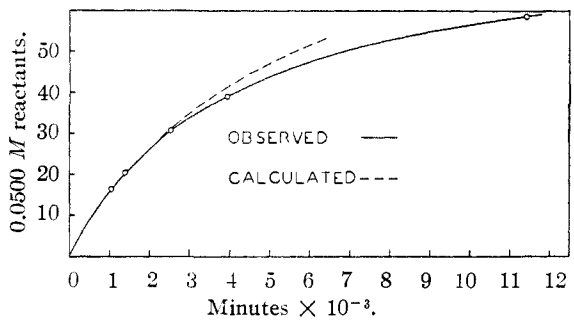


Fig. 3.—*p*-Phenylphenacyl bromide and 4-picoline, 25.95°, 0.0200 *M* reactants.

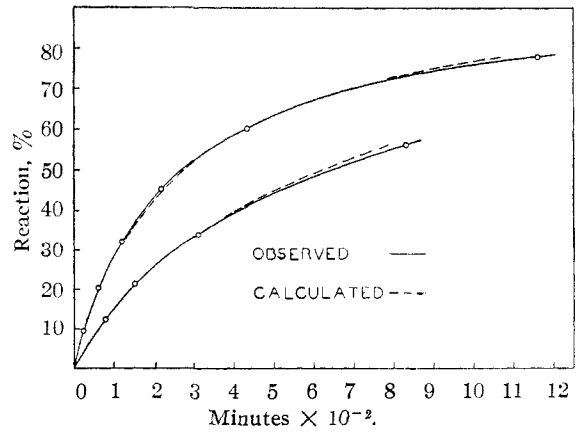


Fig. 4.—*m*-Nitrophenacyl bromide and 4-picoline, 25.95°: upper lines, 0.100 *M* reactants; lower lines, 0.0500 *M* reactants.

by a medium effect; as the relatively polar reactants are used up, the dielectric constant of the medium decreases sufficiently to account for the ap-

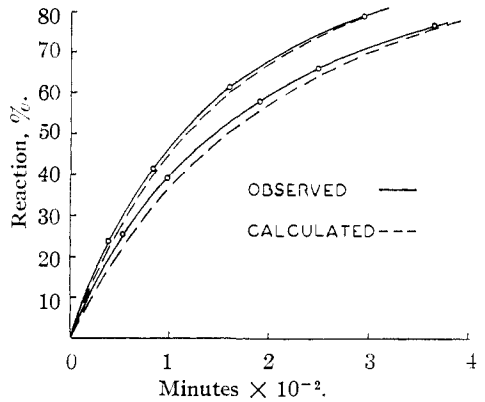


Fig. 5.—*m*-Nitrophenacyl bromide and 4-picoline, 25.95°: upper lines, 0.150 *M* bromide, 0.0500 *M* base; lower lines, 0.0500 *M* bromide, 0.150 *M* base.

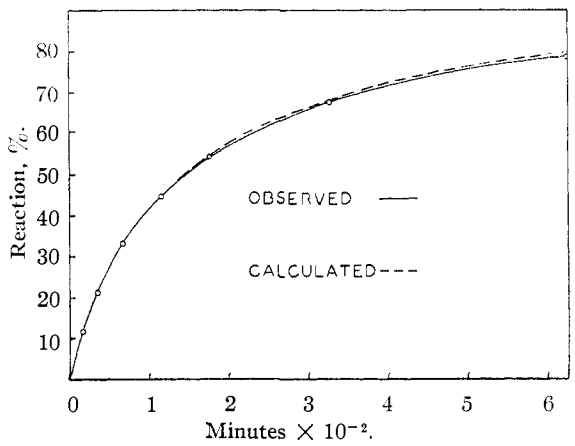


Fig. 6.—*m*-Nitrophenacyl bromide and 4-picoline, 35.35°, 0.100 *M* reactants.

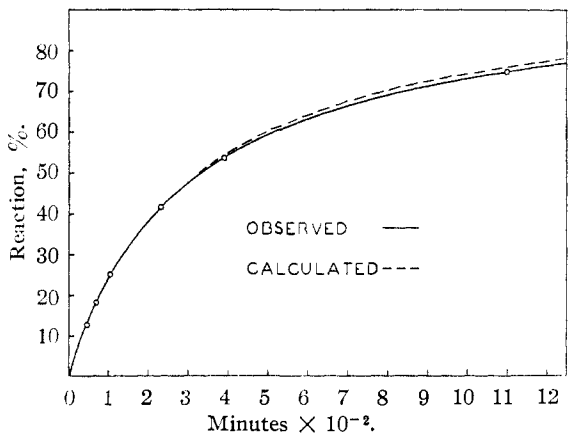


Fig. 7.—*m*-Nitrophenacyl bromide and 4-picoline, 35.35°, 0.0500 *M* reactants.

parent decrease in the rate of the reaction. In order to test this possibility, the reaction of *p*-phenylphenacyl bromide with 4-picoline was run in a solvent mixture containing 1.00 *M* acetone in benzene. This amount of acetone is sufficient to raise the dielectric constant of the medium from 2.3 to approximately 4, and swamp any change due to the reaction. The initial rate of reaction in the mixed solvent is 40% greater than in benzene solution, and

the decrease of the apparent second order rate constant, between 10 and 50% reaction, is approximately 80% of that observed in benzene alone. Since second-order kinetics are not observed in the mixed solvent, it is unlikely that a medium effect is the cause of the deviation from second-order kinetics.

Since the third-order component of the reaction is second order in the concentration of the phenacyl halide, as is clearly demonstrated by Fig. 5, it could be accounted for by a dimerization of the phenacyl halide in benzene solution. Molecular weight measurements by the freezing point depression method in benzene solution showed that both of the phenacyl bromides used in this study were present as the monomers.

It is also possible that the observed kinetic results arise from a first-order decomposition of the product to the reactants superimposed on the second-order reaction leading to the formation of the product. This possibility was eliminated by experiments in which the salts were suspended in benzene at 50°, and recovered quantitatively after a week.

Mechanism

The reaction of tertiary bases with phenacyl halides in benzene solution can be visualized as a combination of two processes: (1) a nucleophilic attack by the base on the carbon atom holding bromine with the establishment of a highly polar transition state complex. Solvation of the transition state complex by one or more molecules of benzene assists the separation of charge required for formation of the product. This process exhibits second-order kinetics, but a molecularity of three or greater because of the participation of solvent molecules in the rate-determining step: (2) the transition state complex if formed as before. The establishment of an electrostatic attraction between the partially negative bromine in the transition state complex and the positively charged end of the carbonyl dipole of a nearby molecule of the phenacyl halide enables the development of a negative charge on the bromide ion and simultaneous formation of the quaternary ammonium cation. This is a third-order process, first order in the concentration of the base and second order in the concentration of the phenacyl halide. These processes are illustrated in Figs. 8 and 9.

The importance of the role of the carbonyl dipole of the phenacyl halide as a solvating agent in the third-order process can be seen in the results obtained with the reaction of 2,4,6-trimethylphenacyl bromide with 4-picoline in benzene solution.[6] The reaction is quite slow at 50°, but is sufficiently rapid that it can be followed to about 40% completion before any discoloration of the solution is noticed.

(6) Baker[4] found that 2,4,6-trimethylphenacyl bromide and pyridine gave no detectable amount of product within five days at 20° in acetone solution. He considered this, together with the inductive effects of groups attached to the ring, as evidence for a mechanism wherein the base attacks the carbonyl carbon, with the establishment of a negative charge on oxygen and a positive charge on nitrogen, followed by a shift of the nitrogen to the adjacent carbon with elimination of bromide coincidental with re-establishment of the carbonyl double bond. It is unlikely that this is the course of the reaction, although the carbonyl dipole is undoubtedly a factor in establishing the proper orientation of the molecules for the reaction.

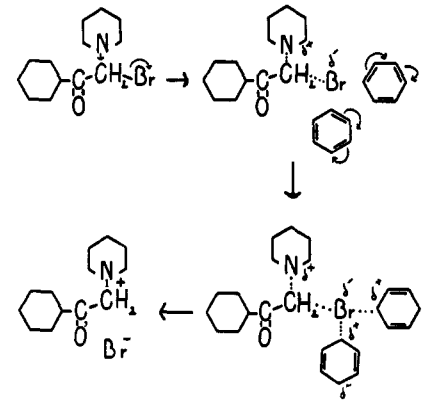


Fig. 8.

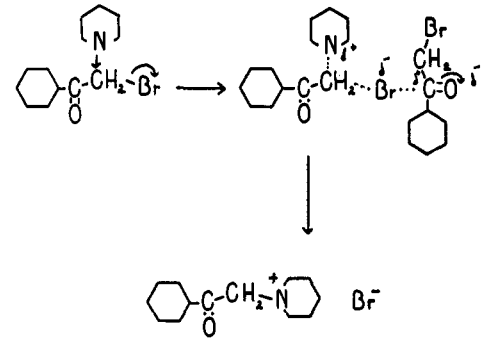


Fig. 9.

The results obtained are shown in Table III. As before, k'_2 and k'_3 represent the rate constants calculated from the second and third order rate equations, respectively.

TABLE III

2,4,6-TRIMETHYLPHENACYL BROMIDE AND 4-PICOLINE, BENZENE SOLUTION, 0.100 *M* REACTANTS, 50°

Time, min.	$a - x$	$10^4\ k'_2$, l./mole-min.	$10^3\ k'_3$, l.^{2}/mole^2-min.
1320	0.0970	2.34	2.37
3150	.0929	2.42	2.52
3650	.0925	2.22	2.30
7200	.0855	2.36	2.54
9220	.0834	2.16	2.40
9600	.0825	2.21	2.45
15750	.0746	2.18	2.54
18450	.0700	2.32	2.82
24270	.0648	2.24	2.85
		Av. 2.27	

As can be seen in Table III, the reaction of 2,4,6-trimethylphenacyl bromide with 4-picoline exhibits second-order kinetics, with the observed values of the second order rate constant distributed in a random manner about the average value. The steady decrease of the second-order rate constant observed when other phenacyl halides are used is not observed here. The effect of the two *ortho* methyl groups in shielding the carbonyl group eliminates the third-order process by preventing the carbonyl group from participating in the solvation step.

Swain and Eddy[2d] have shown that the reaction of methyl iodide with pyridine in benzene solution exhibits second-order kinetics, but the addition of

an electrophilic solvating agent such as phenol accelerates the reaction in proportion to its concentration. Methanol will perform the same function, but less effectively than the more electrophilic phenol; the reagent most effective in solvating the incipient bromide ion, and thereby diffusing the negative charge over a particle appreciably larger than the bromide ion, is the most effective in increasing the rate of reaction. Solvation of the large cation seems to be relatively unimportant, since the quaternization reaction in non-polar solvents has never been observed to have other than a first-order dependence on the concentration of the base, the component which would be capable of solvating a cation.

The phenacyl halide–base system is so constituted that one of the reactants can act as an electrophilic solvating agent. When the second-order process, with solvation performed by the solvent, is sufficiently slow, the third-order process can make an appreciable contribution to the over-all rate. This cannot occur in the quaternization reaction of alkyl halides in benzene, since neither reactant can function as an electrophilic solvating agent. For this reason, the reaction exhibits second-order kinetics if it is homogeneous.

From the data of Table II, the activation energy and entropy of activation of the *m*-nitrophenacyl bromide–4-picoline reaction can be calculated; they are shown in Table IV.

The heat of activation 12.4 kcal. and the entropy of activation −34 e.u. for the second-order process

TABLE IV

m-NITROPHENACYL BROMIDE AND 4-PICOLINE, BENZENE SOLUTION

	E_a, kcal./mole	$\Delta S^{\pm}$, e.u.
Second-order reaction	12.4 ± 0.5	−34 ± 1.5
Third-order reaction	15.6 ± 0.5	−20.6 ± 1.5

are about the same as those generally observed for a second-order quaternization reaction in benzene solution.[2a,7]

For quaternization reactions or in general reactions where ions are produced two generalizations are possible: First, heats of activation do not vary greatly with the solvent; they are if anything greater for the more polar solvents. Second, the entropies of activation are always negative and vary considerably with solvent, becoming more negative as the polarity of the solvent is decreased.[2a,7,8] On the basis of these generalizations the increase in heat of activation and the increase in $\Delta H^{\pm}$ listed for the third-order process as compared to a second-order process are about as expected if the third-order process involves solvation by a ketone, Fig. 9.

Acknowledgment.—We are indebted to the Abbott Fund of Northwestern University for a grant during the course of this work.

(7) F. Ozog, V. Comte and L. C. King, THIS JOURNAL, **74**, 6225 (1952).

(8) Recently R. J. Pearson has discussed a theoretical basis for these generalizations, *J. Chem. Phys.*, **20**, 1478 (1952).

EVANSTON, ILLINOIS

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF G. D. SEARLE AND CO.]

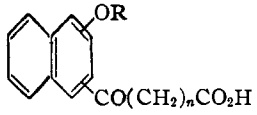
Synthetic Choleretics. II. Phenol Derivatives[1]

BY ROBERT R. BURTNER AND JOHN M. BROWN

RECEIVED AUGUST 13, 1952

A series of cycloalkyl, aryl and aralkyl phenol derivatives bearing the β-carboxypropionyl side chain, as well as some closely related types, were prepared and screened for choleretic activity in the dog. Under experimental conditions several of these compounds were two to four times as active as dehydrocholic acid.

In the first paper[2] of this series it was shown that certain keto acid derivatives of α- or β-naphthol having the general formula

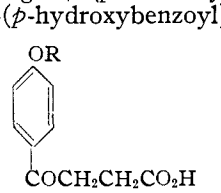


R = H or CH_3
n = 2–8

will increase the volume output of bile in dogs. Among the twenty-four compounds reported at that time, those bearing the β-carboxypropionyl side chain (–$COCH_2CH_2CO_2H$) were found to be especially effective choleretics. The most potent compound tested was β-(1-methoxy-4-naphthoyl)-propionic acid. This material not only produced a greater acute response than any other member of the series, but also manifested a longevity of action quite singular at that time.

In view of the foregoing results, it seemed advisable to extend the evaluation of choleretic activity to other phenolic, binuclear ketoalkanoic acids, particularly those closely related to β-(1-methoxy-4-naphthoyl)-propionic acid. Furthermore, a comparison of the activities of the free phenolic compounds with those of the corresponding methyl ethers was indicated.

Although β-(*p*-methoxybenzoyl)-propionic acid and β-(*p*-hydroxybenzoyl)-propionic acid themselves exhibit relatively feeble choleretic properties,[3] their structural relationship to the more



R = CH_3 or H

(1) Presented before the Division of Medicinal Chemistry of the American Chemical Society in September, 1950, at Chicago, Illinois.

(2) R. R. Burtner and J. M. Brown, THIS JOURNAL, **73**, 897 (1951).

(3) M. J. Gunter, K. S. Kim, D. F. Magee, H. Ralston and A. C. Ivy, *J. Pharmacol.*, **99**, 465 (1950).