geometric isomers, show a difference in their pharmacological properties as well as in their physical properties. As nearly as can be judged they show about the same effect on the rabbit's cornea, but the durations of anesthesia produced by intracutaneous injection into the guinea pig and the subcutaneous and intravenous toxicities are markedly different. It should be noted that the less stable isomer (*i. e.*, the lower-melting one) is the more active physiologically.

Summary

1. A method for the isolation of γ-picoline from coal tar bases has been described.
2. A number of new substituted piperidino-alkyl benzoates have been prepared.
3. All of these substances are local anesthetics. Certain of the phenylalkyl substituted derivatives are unusually potent anesthetics, producing anesthesia of the rabbit's cornea for a period of five to six days.
4. Some relationships between structure and pharmacological action are discussed.

MADISON, WISCONSIN

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

COMPARATIVE REACTIVITIES OF SOME SUBSTITUTED BENZYL HALIDES[1]

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RECEIVED DECEMBER 20, 1929 PUBLISHED APRIL 7, 1930

The present investigation is a study of the influence of substitution in the aromatic nucleus upon the reactivity of the benzyl halides. The metathetical reaction which has been chosen for investigation is that which occurs between the benzyl halides and an alkali sulfite, a reaction which has been used considerably in organic chemistry since its early discovery by Strecker,[3] and which occurs with an easily measurable speed at ordinary temperatures. The products of the reaction are a benzyl sulfonate and an inorganic halide.

The results of previous investigations of the velocity of replacement of halogen in the benzyl halides are not entirely concordant. Concordancy, in fact, may hardly be expected at present, in view of the complexity of this sort of problem, an insufficient understanding, as yet, of the more fundamental physico-chemical relationships involved, and the present sparsity of accurate experimental data. For the sake of brevity,

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[1] Presented, in part, at the Minneapolis meeting of the American Chemical Society, September, 1929.

[2] National Research Fellow in Chemistry.

[3] Strecker, *Ann.*, **148**, 90 (1868).

the results of previous researches have been condensed into the form of a table (Table I). The important relationships may here be noted at a glance. Only a few additional comments need be made in order to accentuate a few relationships which cannot be made evident in the table.

Slator and Twiss,[4] who studied the reaction between some benzyl chlorides and sodium thiosulfate, used iodine titrations to follow the course of their reaction. They later found[5] that iodine reacted with alkyl thiosulfates, giving rise to sulfides and disulfides. In the interpretation of their results, they seem to take no account of this disturbance.

Conant, Kirner and Hussey[6] investigated the reactivity of a few benzyl chlorides as a part of a much more exhaustive study of the reactivity of alkyl halides. An increase in reactivity toward potassium iodide of three- to nine-fold was observed when a nuclear nitro group or chlorine atom was present. However, a surprisingly greater reactivity was noted when a nuclear bromine atom was introduced. Both the ortho and the para isomer (the meta compound was not studied) reacted some two to three hundred times as rapidly as benzyl chloride itself. (No explanation was advanced for this apparently anomalous behavior. In all the other reactions listed in Table I, differences in reactivity brought about by nuclear substitution never exceeded several fold.)

The most exhaustive of the researches listed is that of Olivier,[7] who subjected these compounds to hydrolyis by means of aqueous alcohol (and later by means of aqueous acetone). The general results of this work indicated that a substituent has the same effect upon a side-chain chlorine atom that it has upon a nuclear hydrogen atom. That is, in case the nuclear substituent was a meta orienting group (a group decreasing the velocity of substitution of a nuclear hydrogen) the speeds of hydrolysis of isomeric substituted benzyl chlorides were in the order meta, ortho, para. When ortho–para orienting groups (groups which increase the velocity of substitution of nuclear hydrogen) were present, the order of reactivity of isomers toward aqueous alcohol was para, ortho, meta. In the theoretical papers of Olivier, and of Olivier and Berger, the conclusions were reached that steric factors played no part in these reactions; but that the results, with the exception of those of the ortho-substituted compounds, might be explained by considerations based upon the theory of alternate polarity of carbon compounds.

It may readily be seen that at the present time no extremely safe generalization may be made. It may be noted, however, that in all these reactions

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[4] Slator and Twiss, *J. Chem. Soc.*, **95**, 93 (1909).

[5] Price and Twiss, *ibid.*, **95**, 1489 (1909); Twiss, *ibid.*, **105**, 1672 (1914).

[6] Conant, Kirner and Hussey, THIS JOURNAL, **47**, 488 (1925).

[7] Olivier, *Rec. trav. chim.*, **41**, 301, 646 (1922); **42**, 516, 775 (1923); **45**, 296 (1926); Olivier and Berger, *ibid.*, **45**, 452 (1926); **46**, 609, 861 (1927); Olivier, *ibid.*, **48**, 227 (1929).

TABLE I

COMPARATIVE REACTIVITIES OF THE BENZYL HALIDES

Halides	Reagent	Nuclear substituent	Order of reactivity (un = unsub. halide)
Chlorides	Sodium thiosulfate in aqueous alcohol[4,5]	NO_2	*p*>*m*>*o*=un
Bromides	Aqueous alcohol[8]	OCH_3	*p*>*o*>un>*m*
		CH_3	*p*>*o*>*m*>un
		F	*p*>un>*o*>*m*
		Cl	un>*p*>*o*>*m*
		Br	un>*p*>*o*>*m*
		COOH	un>*m*>*p*
Bromides	HI in alcohol[8]	OCH_3	*m*>un>*o*>*p*
		CH_3	*m*>*o*>*p*>un
		F	*o*>*m*>un>*p*
		Cl	un>*p*>*o*>*m*
		Br	un>*p*>*o*>*m*
		COOH	un>*p*>*m*
Chlorides	Sodium ethylate in absolute alcohol[9]	CH_3	*o*>*p*>*m*>un
		Cl	*p*>*m*>*o*>un
		Br	*m*>un>*o*
Chlorides	KI in acetone[6]	NO_2	*o*>*p*>*m*>un
		Cl	*o*>*p*>un
		Br	*o*>*p*>un
Chlorides	Aqueous alcohol[7] (and aqueous acetone)	CH_3	*p*>*o*>*m*>un
		NO_2	un>*m*>*o*>*p*
		Cl	un>*p*>*o*>*m*
		Br	un>*p*>*o*>*m*
		I	un>*p*>*o*>*m*
		COOH	un>*m*>*p*

except that of reduction with hydriodic acid,[8] ortho and para compounds were nearly always more reactive than the corresponding meta isomers. The ω-halogeno-toluic acids provided an exception to this order, and the nitrobenzyl chlorides in the case of the hydrolysis reaction of Olivier.[7] It should be mentioned that in the latter case the differences in reactivity of the isomeric nitro compounds were exceedingly small; the actual velocity constants at 83° were 0.0014, 0.0013 and 0.0011.

The present investigation was initiated primarily with the purpose of obtaining additional careful data. In this sort of work, theoretical deductions may most safely be made only when a large number of facts are available upon which to base these deductions.

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[8] Lapworth and Shoesmith, *J. Chem. Soc.*, **121**, 1391 (1922); Shoesmith, *ibid.*, **123**, 2828 (1923); Shoesmith, Hetherington and Slater, *ibid.*, **125**, 1312 (1924); Shoesmith and Slater, *ibid.*, **125**, 2278 (1924); *ibid.*, 214 (1926); Shoesmith and Taylor, *ibid.*, 2832 (1926); Shoesmith and Connor, *ibid.*, 1768 (1927).

[9] Franzen, *J. prakt. Chem.*, [2] **97**, 82 (1918); Franzen and Rosenberg, *ibid.*, [2] **101**, 333 (1920).

Materials

Sodium sulfite crystals were obtained from Mallinckrodt. They were recrystallized twice from water and dried in an oven at 120°.

Benzyl chloride was obtained from Eastman. It was fractionated at atmospheric pressure and the fraction boiling at 178–179° was refractionated under vacuum. The fraction boiling at 81.5–82° at 28 mm. was used.

The following substances, obtained from the Eastman Kodak Company, were purified by fractionation under vacuum: *o*-chlorobenzyl chloride, b. p. 105–107° at 28 mm.; *p*-chlorobenzyl chloride, b. p. 113–115° at 24 mm.; *o*-bromobenzyl chloride, b. p. 117–119° at 21 mm.; *o*-chlorobenzyl bromide, b. p. 118–119° at 19 mm.

The following substances, obtained from Eastman, were purified by crystallization, as shown: *p*-bromobenzyl chloride, from 95% alcohol and from petroleum ether, m. p. 47.5–48°; *p*-nitrobenzyl chloride, three times from petroleum ether, m. p. 73.5–74.5°; *p*-chlorobenzyl bromide, twice from alcohol, m. p. 50.5–51.5°; *p*-nitrobenzyl bromide, twice from a mixture of alcohol and petroleum ether, m. p. 98.5–99°; *o*-nitrobenzyl chloride was obtained from Eimer and Amend. It was recrystallized from alcohol and from a mixture of alcohol and petroleum ether; m. p. 48.7–49.2°.

***m*-Bromobenzyl Bromide.**—*m*-Bromobenzoic acid was reduced electrolytically, according to the method of Mettler.[10] The *m*-bromobenzyl alcohol thus obtained was treated with one molar equivalent of phosphorus tribromide. The bromide obtained boiled at 112–114° at 6 mm. It was recrystallized from a mixture of petroleum ether and alcohol; m. p. 42–42.4°.

***m*-Bromobenzyl Chloride.**—From *m*-bromobenzyl alcohol and thionyl chloride; purified by vacuum fractionation; b. p. 120–122° at 18 mm.

***m*-Chlorobenzyl Bromide.**—The alcohol was obtained in 89% yield by electrolytic reduction according to Mettler.[10] From it the bromide was obtained in 83% yield by the action of one molecular equivalent of phosphorus tribromide. It was purified by vacuum fractionation; b. p. 110–111° at 12 mm.

***m*-Chlorobenzyl Chloride.**—From the alcohol in 78% yield by treatment with thionyl chloride; purified by vacuum fractionation; b. p. 111–113° at 25 mm.

***o*-Nitrobenzyl Bromide.**—Twenty-five grams of *o*-nitrobenzaldehyde was converted to the alcohol by 15 g. of potassium hydroxide in 75 g. of water. The alcohol was treated with phosphorus tribromide, giving 60% of the theoretical quantity of the bromide, calculated on the basis of the aldehyde used. The bromide was recrystallized from alcohol, from a mixture of alcohol and petroleum ether, and from petroleum ether; m. p. 45.8–46.3°.

***m*-Nitrobenzyl Bromide.**—The alcohol was obtained by running a Cannizzaro reaction on *m*-nitrobenzaldehyde, and was converted to the bromide by phosphorus tribromide; b. p. 162–163° at 13 mm. It was then recrystallized from petroleum ether containing alcohol; m. p. 57° (sharp).

***m*-Nitrobenzyl Chloride.**—Ten and five-tenths grams of *m*-nitrobenzyl alcohol (obtained as above) gave 10.5 g. of *m*-nitrobenzyl chloride when treated dropwise with thionyl chloride; b. p. 173–174° at 34 mm. It was recrystallized from petroleum ether containing a little alcohol; m. p. 45.5–46.5°.

Method

The present experiments have been carried out in 50% (by weight) aqueous alcohol. Volumetric flasks were used for reaction vessels. The reactions were started by rapidly adding a known volume of a solution

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[10] Mettler, *Ber.*, **38**, 1749 (1905).

of sodium sulfite in 50% alcohol to a weighed quantity of the organic halide.[11] At desired intervals aliquot portions were withdrawn by means of calibrated, fast-flowing pipets. In the case of the benzyl bromides, these portions were run into excess standard iodine solution and the excess iodine titrated with standard thiosulfate. Parallel runs were made upon benzyl bromide, using two different methods, as follows: in the first of these the above procedure was followed; in the second case the withdrawn samples were simply run into cold water and the titrations were then rapidly accomplished, using standard iodine solution directly. The velocity constants thus obtained (5.86 and 6.12) checked within about 4%. It is therefore evident that in the case of the benzyl chlorides, where the mean reaction speeds are about forty times smaller than those of the benzyl bromides, there is no appreciable error involved in the second method of measurement. All subsequent runs upon the benzyl chlorides were, therefore, carried out according to this procedure, wherein the withdrawn samples were run into cold water and the unused sulfite was titrated rapidly with standard iodine solution.

The reactions follow the bimolecular law within experimental error (considered to be 5–8%). Bimolecular velocity constants were calculated on the basis of the time of mixing as zero time, unless the organic halide did not dissolve rapidly; the zero time was then taken as the time of the first withdrawal of a sample after true homogeneity was attained.

Preliminary Experiments Relative to the Reaction Mechanism

Qualitative Estimation of Sulfonate Formed.—That the products formed by the action of sodium sulfite upon various benzyl chlorides and bromides are actually the corresponding sodium sulfonates has been demonstrated by Clutterbuck and Cohen.[12]

Several of these experiments were repeated, and it was ascertained

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[11] Prepared solutions of the organic halide were not used, in order to minimize any hydrolysis or alcoholysis which might occur through the interaction of the organic compound and the mixed solvent. A small amount of alcoholysis or hydrolysis must necessarily occur during the reaction, but this factor is known to be entirely negligible in its influence upon the present results from the fact that the velocity constant of the hydrolysis of benzyl chloride by 50% alcohol [Olivier, *Rec. trav. chim.*, **41**, 301 (1922)] is nearly 1000 times smaller than the velocity constant found for the above replacement reaction. Direct experiments which confirmed this are described in a later part of this paper.

[12] Clutterbuck and Cohen, *J. Chem. Soc.*, **123**, 2507 (1923). For other applications of the Strecker reaction to benzyl compounds, see Eugene Fischer, German patent 48,722, *Friedländer*, **2**, 98 (1888); Marckwald and Frahne, *Ber.*, **31**, 1855 (1898); Böhler, *Ann.*, **154**, 51 (1870); Dahl and Company, German patent 55,138, *Friedländer*, **2**, 386 (1889); Mohr, *Ann.*, **221**, 216 (1884); Weiss and Reiter, *ibid.*, **355**, 177 (1907); Bonomi da Monte and Zoso, *Gazz. chim. ital.*, **27**, II, 469 (1897); Purgotti and Monti, *ibid.*, **30**, II, 247 (1900); Purgotti and Lunini, *ibid.*, **33**, II, 334 (1903).

that 80–90% yields of benzyl sulfonates could be obtained by the usual methods of separation.

Oxidizing Action Due to the Organic Halide.—In the case of some alkyl halides the reaction with alkali sulfites leads to a certain amount of reduction to hydrocarbons and the formation of the corresponding quantity of sulfate. To see to what extent the present reaction was complicated by this factor, the sulfate present in 25 cc. of the sulfite solution at the beginning of a reaction with benzyl chloride and that present in 25 cc. of the reaction mixture after the reaction had run for six hours were precipitated as barium sulfate, with the following results.

Detectable in the unused solution, 0.1074 and 0.1045 g. of $BaSO_4$.

Detectable in the used solution, 0.1038 and 0.1044 g. of $BaSO_4$. Any oxidation due to the organic compound or due to air (auto-oxidation of the sulfite solution certainly does occur to some extent) is therefore of negligible consequence.

Auto-oxidation of the Sulfite Solution.—The amount of this occurring during an actual run has just been shown to be negligible. However, a slight amount does take place, as is shown by the following data. Twenty-five-cc. portions of different sulfite solutions were titrated with iodine before the start of a reaction, and again several hours later.

Initial iodine titer, cc.	33.87	35.90	43.20
Final iodine titer, cc.	33.51	35.40	42.90
Time elapsed, hours	6	8	9

The error due to this change was minimized by determining the initial iodine titer immediately before each run was started.

Extent of Hydrolysis and Alcoholysis.—Parallel runs were made in which the course of the reaction was followed on the one hand by iodine titration and on the other by titrations with hydrochloric acid in the presence of methyl red as indicator. Any formation of strong acid, due to either of the above reactions, should be evidenced by an increase in the ratio of iodine to hydrochloric acid required by equal amounts of the reaction mixtures at equivalent times. This ratio actually remained constant within titration error during the first 80% of the reaction. During the last 20% it increased somewhat. Two or three per cent. of strong acid (estimated on the basis of the initial reactants) was present after seventy hours, when the reaction was virtually complete.

Variation of the Velocity Constant with the Initial Concentration of the Reactants.—Experiments were made with benzyl chloride to determine the effect of variations in the initial concentrations of the reacting substances, and also to ascertain the effect of varying the ratio of the concentration of sulfite to benzyl halide. A summary of these results is given in Table II. There was a considerable range over which the velocity constant did not vary except within the experimental error (5–8%). At higher concentrations, however, there was noted a decrease in the velocity constant; and at very low initial concentrations the values increased markedly. When the initial concentrations were about 18 × 10^{-3} mole per liter, the normal value of 0.391 had increased to 0.430, and had further increased to 0.536 when the initial concentrations were 12.7 × 10^{-3} mole per liter. From Table II it is also evident that the velocity constant depends about as much upon the initial concentration of one reactant as upon the other. Thus, when the initial concentration of either reactant was about 12.5 × 10^{-3}, while that of the other was within the "normal range," that is, about 24 × 10^{-3}, the calculated constants also fell within the normal range. It is certain that the variations are no greater than 8% when the concentrations of both reactants lie between 40 × 10^{-3} and 20 × 10^{-3} mole per liter. Therefore, in all runs made for the determination of comparative reactivities, the initial concentrations of both reacting substances were taken so as to be well within this range, and the values obtained are, therefore, strictly comparable within the general limit of accuracy permitted by the experimental technique employed.

Table II

Variation of the Velocity Constant with the Initial Concentration of the Reactants

A, concn. of benzyl chloride (moles/liter). B, concn. of sodium sulfite (moles/liter). Temp., 40.00 ± 0.03°

No.	$A \times 10^{-3}$	$B \times 10^{-3}$	K_{mean} (bimol.)
1	90.3	45.2	0.320
2	62.0	28.1	.388
3	57.5	28.1	.381
4	40.9	40.3	.398
5	33.2	33.7	.386
6	33.1	33.3	.408
7	29.9	29.9	.381
8	27.4	26.8	.397
9	22.8	23.4	0.376
10	20.4	34.2	.395
11	23.8	12.12	.408
12	12.56	24.20	.396
13	18.24	18.24	.430
14	12.70	12.70	.536
15	11.48	8.72	.615

Average of 2–12, 0.392.

The Effect of Variations in *P*H.—Parallel experiments were carried out with benzyl chloride in which the *P*H of the solution was varied by using sodium sulfite alone, sodium sulfite buffered by sodium acetate, and sodium bisulfite. The calculated velocity constants were 0.386, 0.370 and 0.006. When an equimolecular mixture of sodium sulfite and sodium bisulfite was used, the calculated "constants" decreased from 0.180 to 0.04 within a given run, as the reaction proceeded. It appears, therefore, that the reaction actually occurs between the organic halide and sulfite ion as follows: $RCH_2X + SO_3^{=} \longrightarrow RCH_2SO_3^- + X^-$. In the case of the sulfite–bisulfite mixture, the *P*H of the solution changes as the reaction proceeds, due to the reversible change of sulfite into bisulfite ions, and since there is available no real measure of the sulfite-ion concentration, no proper velocity constants may be calculated. In the case of the sulfite, the bisulfite or the sulfite–acetate, the *P*H of the solution must remain nearly constant, and, therefore, the concentration (or activity) of sulfite ion is proportional, within a few per cent., certainly, to the total concentration of the molecular species. In the case of sodium sulfite alone, the sulfite ion activity is probably, within a small error, equal to the total concentration of sodium sulfite molecules. (Any differentiation between "concentration" and "activity" is necessarily meaningless as far as the present results extend.)

Addition of sodium hydroxide to the reaction mixture causes the velocity "constants" to fall off rapidly within a run. This is undoubtedly due to side reactions which occur with appreciable speeds in an alkaline medium. These side reactions may be the formation of benzyl alcohol, or of stilbene, or both, since both reactions are known to occur to some extent in a medium of sufficient alkalinity.[13]

Discussion of the Results

A few typical experiments are reproduced in Table III. For the benzyl chlorides there is no noticeable drift in the values of the velocity constants during the first 75% of the reaction. The agreement within a given run is all that could be expected. For the benzyl bromides, where the reaction speeds are about forty times faster, the velocity constants show no perceptible drift during the first 90% of the reaction. In all cases the mean values were reproducible to within 8% and usually to within 4–5%.

TABLE III

TYPICAL DATA CONCERNING THE REACTION BETWEEN SOME BENZYL HALIDES AND SODIUM SULFITE IN 50% AQUEOUS ALCOHOL

Benzyl chloride at 40.00 ± 0.03°

Benzyl chloride, 0.04088 *M;* sodium sulfite, 0.04032 *M;* titrations (25 cc.) with 0.02316 *M* iodine

Time, minutes	Iodine, cc.	*K* (bimol.)
0.0	43.55	...
30.5	28.97	0.403
59.5	21.94	.403
105.5	15.83	.400
165.5	11.85	.388
255.5	8.24	.398
		Av. .398

o-Chlorobenzyl chloride at 40.00 ± 0.03°

o-Chlorobenzyl chloride, 0.02936 *M;* sodium sulfite, 0.02920 *M;* titrations (25 cc.) with 0.02300 *M* iodine

Time, minutes	Iodine, cc.	*K* (bimol.)
0.0	31.84	...
15.0	27.77	0.333
35.5	23.78	.328
70	19.17	.325
120	14.98	.323
140	13.86	.319
210	10.71	.323
330	7.42	.338
		Av. .328

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[13] Shoesmith and Slater, *J. Chem. Soc.*, **125**, 2287 (1924); Acree, *Am. Chem. J.*, **29**, 593 (1903); Tschitschibabin, *Chem. Zentr.*, I, 1301 (1902); Staudinger and Kupfer, *Ber.*, **44**, 2194 (1911); Bergmann and Hervey, *ibid.*, **62**, 900 (1929).

TABLE III (*Concluded*)

m-Chlorobenzyl bromide at 30.00 ± 0.03°

m-Chlorobenzyl bromide, 0.03020 *M;* sodium sulfite, 0.03020 *M;* titrations (25 cc.) with 0.02231 *M* iodine and 0.03452 *M* $Na_2S_2O_3$

Time, minutes	Iodine, cc.	$Na_2S_2O_3$ cc.	*K*
0	39.97	7.88	..
4.5	26.57	3.00	2.94
10	19.98	2.20	2.84
15	20.17	7.48	3.00
25	15.01	6.26	3.08
35	15.10	9.26	3.08
50	15.05	11.05	2.96
70	14.95	13.37	3.04
		Av.	3.00

o-Nitrobenzyl bromide at 30.00 ± 0.03°

o-Nitrobenzyl bromide, 0.03530 *M;* sodium sulfite, 0.03530 *M;* titrations (37.5 cc.) with 0.02231 *M* iodine and 0.03452 *M* $Na_2S_2O_3$

Time, minutes	Iodine, cc.	$Na_2S_2O_3$, cc.	*K*
0	59.10	0.00	...
3	39.87	1.76	10.13
7	31.14	6.40	10.20
12	19.97	2.30	10.60
20	15.07	3.34	10.53
30	15.04	7.83	10.60
45	15.06	11.54	10.81
		Av.	10.48

The average velocity constants at 40° for the benzyl chlorides are summarized in Table IV. From this it may be seen that a nuclear nitro group increases the reactivity of the halide toward sodium sulfite regardless of its position. The greatest effect is produced when the nitro group is present in the para position, and the smallest effect when it is introduced into the meta position. A nuclear chloro or bromo atom causes a decrease in the reactivity toward sulfite ions in every case except that of the *p*-bromo compound.[14] In both cases the para isomer is the most reactive, the ortho isomer next, and the meta isomer has the lowest reactivity. The order is thus the same as that found in the case of the nitro derivatives. The results obtained when working with the benzyl bromides are summarized in Table V. The bromides conform to the same general relationships as the chlorides. A nuclear chlorine atom decreases the rate of replacement, whereas a nitro group increases the reactivity in this reaction. In both cases the relative reactivities of a group of isomers is para > ortho > meta, parallel with that of the benzyl chlorides. *m*-Bromobenzyl bromide is less reactive than benzyl bromide. (In this case the ortho and para isomers were not investigated.) The reaction velocities of the halogen compounds are in the same order at 40° as at 30°. The temperature coefficients vary, however, from 1.90 for the *m*-bromo compound to 3.18 for benzyl bromide itself.

The present results are in agreement with the generalization previously

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[14] This is an anomalous effect for which there is, at present, no adequate explanation. The actual value of the velocity constant, however, was carefully checked. Two separate runs upon a product which had been purified by crystallization first from alcohol and then from petroleum ether gave values of 0.453 and 0.468. The substance was then recrystallized from alcohol and from benzene. The melting point was raised half a degree by this procedure. The average value of the velocity constant obtained when using the repurified substance was, however, 0.477, or within 4% of the previous average.

TABLE IV

RELATIVE REACTION RATES OF BENZYL CHLORIDES WITH SODIUM SULFITE (TEMP., 40.00 ± 0.03°)

Benzyl chloride cpd.	K_{mean} (bimol.)
Benzyl chloride	0.392
p-Chloro-	0.345
o-Chloro-	.328
m-Chloro-	.238
p-Bromo-	.465
o-Bromo-	.262
m-Bromo-	.238
p-Nitro-	.738
o-Nitro-	.525
m-Nitro-	.487

For benzyl chloride at 30.00°, K = 0.169. Temp. coeff., 2.32.

TABLE V

RELATIVE REACTION RATES OF BENZYL BROMIDES WITH SODIUM SULFITE

Compound	40.00 ± 0.03° K_{mean} (bimol.)	30.00 ± 0.03° K_{mean} (bimol.)	Temp. coeff.
Benzyl Bromide	5.86	18.6	3.18
p-Chloro-	5.17	14.2	2.75
o-Chloro-	3.84	8.67	2.26
m-Chloro-	3.00	7.16	2.38
m-Bromo-	3.40	6.42	1.90
p-Nitro-	17.2		
o-Nitro-	10.5		
m-Nitro-	9.55		

made, on the basis of a résumé of the previously existing literature, that in nuclear substituted benzyl halides ortho and para isomers usually show a greater reactivity toward replacement reagents than the corresponding meta isomer. The consistency of the relative order of reactivity of isomers (para > ortho > meta) found for this replacement reaction was, however, not to be anticipated.

Summary

1. A kinetic study has been made of the replacement reaction between some substituted benzyl halides and sodium sulfite in 50% aqueous alcoholic solution. The reactions are bimolecular. In the case of benzyl chloride the calculated velocity constants increased as the initial concentrations of the reactants were decreased.

2. The introduction of a nuclear nitro group into benzyl chloride or bromide increased the speed of this reaction, regardless of position. A nuclear chlorine or bromine atom decreased the speed of the reaction, except in the case of *p*-bromobenzyl chloride. This compound reacted considerably faster than benzyl chloride.

3. The order of reactivity of isomers was in all cases, para > ortho > meta.

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