Intramolecular Nucleophilic Participation. IX.
Solvolysis of o- and p-Thiolcarbophenoxybenzyl Bromides

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In 80% aqueous dioxane o-thiolcarbophenoxybenzyl bromide hydrolyzes significantly faster than does its para isomer (8.11 times at 65°). In acetic acid at 85° the ortho/para solvolysis rate constant ratio is exceptionally high (534) when compared with that for the o- and p-methoxybenzyl bromides (0.0017 at 60°), a system in which ortho substituent participation does not occur. The high reactivity of o-thiolcarbophenoxybenzyl bromide is attributed to the favorable influence of the S atom on the capacity of the o-COSC$_6$H$_5$ group to function as an internal nucleophile. The rate influence of the substituent becomes larger as the medium becomes less nucleophilic in character.

Both o-carbophenoxy and o-nitro substituents function as internal nucleophiles in promoting the hydrolysis and also the acetolysis of benzhydryl bromide.[1-3] However, these substituents participate much less effectively in benzyl halide hydrolysis.[1,2,4] Presumably in the reactions of the benzyl systems in question the geometry at the transition state provides for substantial dispersal of positive charge at the reaction center through delocalization of ring π electrons rather than through involvement of the neighboring ortho substituents.[1,4]

Recently it has been reported that the acetolysis of o-dithiacyclopentylbenzyl chloride is subject to pronounced rate enhancement through participation of the –CH(SCH$_2$)$_2$ group.[5] Apparently when, as in this case, the ortho substituent contains a strongly nucleophilic atom (S) at a proper distance from the reaction center, the geometry at the transition state is such that the influence of that substituent on reactivity is appreciable.

To explore further the matter of the effectiveness of sulfur containing ortho nucleophiles as participants in the solvolysis of benzyl halides, a comparison has been made of the hydrolysis and acetolysis rates of the o- and p-carbophenoxy- and o- and p-thiolcarbophenoxybenzyl bromides. In the acetolysis reactions a dramatic difference in the capacities of o-COOC$_6$H$_5$ and o-COSC$_6$H$_5$ to serve as internal nucleophiles has been observed.

Experimental Section

Analytical Procedures.—Melting points and boiling points are uncorrected. Nuclear magnetic resonance spectra were obtained using a Varian Associates Model A-60A instrument. Microanalyses were performed by Mr. V. Tashinian and Associates, Berkeley, Calif.

Materials.—Benzyl bromide (Eastman Organic Chemicals) was distilled under reduced pressure prior to use.

To prepare the o- and p-carbophenoxytoluenes, a stoichiometric quantity of thionyl chloride was added slowly to a solution of o- or p-toluic acid (Eastman Organic Chemicals), respectively, in pyridine solvent. When the reaction mixture had cooled to room temperature, a stoichiometric amount of phenol was added and the mixture was heated on a steam bath for ca. 2 hr in a system protected from atmospheric moisture. The reaction mixture was diluted with water and extracted with ether. The products were

obtained in 85% yield upon work-up of the ether solutions: o-carbophenoxytoluene, bp 117–118° (0.6 mm) [lit.[6] bp 306° (754 mm)]; p-carbophenoxytoluene, mp 77–79° (lit.[6] mp 83°).

The o- and p-carbophenoxybenzyl bromides were prepared through the benzoyl peroxide induced reaction of equimolar quantities of N-bromosuccinimide and o- or p-carbophenoxytoluene, respectively, in carbon tetrachloride solvent at reflux temperature. Recrystallization of both isomers from mixed hexanes gave white crystals in ca. 50% yield. o-Carbophenoxybenzyl bromide had mp 51–52.5°; nmr (CCl$_4$) δ 4.92 (s, 2, CH$_2$), 7.32 (m, 8, arom), and 8.11 ppm (m, 1, arom, ortho to C=O).

Anal. Calcd for C$_{14}$H$_{11}$BrO$_2$: C, 57.75; H, 3.82; Br, 27.45. Found: C, 57.76; H, 3.72; Br, 27.58.

p-Carbophenoxybenzyl bromide had mp 93–95°; nmr (CCl$_4$) δ 4.40 (s, 2, CH$_2$), 7.30 (m, 7, arom), and 8.10 ppm (m, 2, arom, ortho to C=O).

Anal. Calcd for C$_{14}$H$_{11}$BrO$_2$: C, 57.75; H, 3.82; Br, 27.45. Found: C, 57.65; H, 3.90; Br, 27.60.

To prepare p-thiolcarbophenoxytoluene, 9.0 g of thionyl chloride was added slowly to a solution of 10 g of p-toluic acid (Eastman Organic Chemicals) in 35 ml of dry pyridine in a system protected from atmospheric moisture. When the reaction mixture had cooled to room temperature, 8.2 g of thiophenol was added slowly and the mixture was heated on a steam bath for ca. 2 hr. Approximately 100 ml each of ether and water were added to the cooled reaction mixture, and the ether layer was washed successively with water, dilute hydrochloric acid, water, 3 N sodium hydroxide, and water. The ether solution was dried (Na$_2$SO$_4$) and concentrated. Recrystallization of the residual solid from ca. 100 ml of mixed hexanes provided 12 g (71%) of p-thiolcarbophenoxytoluene as white crystals: mp 91–93°; nmr (CCl$_4$) δ 2.40 (s, 3, CH$_3$), 7.29 (m, 7, arom), and 7.88 ppm (m, 2, arom, ortho to C=O).

Anal. Calcd for C$_{14}$H$_{12}$OS: C, 73.65; H, 5.31; S, 14.04. Found: C, 73.48; H, 5.25; S, 13.94.

o-Thiolcarbophenoxytoluene was prepared from o-toluic acid (Eastman Organic Chemicals), thionyl chloride, and thiophenol in 69% yield by much the same procedure described for the synthesis of the para isomer: mp 45–47°; nmr (CCl$_4$) δ 2.44 (s, 3, CH$_3$), 7.33 (m, 8, arom), and 7.89 ppm (m, 1, arom, ortho to C=O).

Anal. Calcd for C$_{14}$H$_{12}$OS: C, 73.65; H, 5.31; S, 14.04. Found: C, 73.73; H, 5.16; S, 14.01.

The o- and p-thiolcarbophenoxybenzyl bromides were synthesized through the light-induced reaction of equimolar quantities of N-bromosuccinimide and o- or p-thiolcarbophenoxytoluene, respectively, in carbon tetrachloride solvent. The crude products from the preparation of both isomers were contaminated with a significant quantity of the corresponding dibromide. The pure monobromides were obtained in ca. 30% yield by fractional recrystallization from mixed hexanes–carbon tetrachloride mixed solvent. o-Thiolcarbophenoxybenzyl bromide had mp 92–94°; nmr (CCl$_4$) δ 4.72 (s, 2, CH$_2$), 7.46 (m, 8, arom), and 7.92 ppm (m, 1, arom, ortho to C=O).

Anal. Calcd for C$_{14}$H$_{11}$BrOS: C, 54.73; H, 3.62; Br, 26.01; S, 10.44. Found: C, 54.53; H, 3.66; Br, 26.28; S, 10.37.

p-Thiolcarbophenoxybenzyl bromide had mp 96–99°; nmr (CCl$_4$) δ 4.42 (s, 2, CH$_2$), 7.48 (m, 7, arom), and 7.95 ppm (m, 2, arom, ortho to C=O).

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Anal. Calcd for $C_{14}H_{11}BrOS$: C, 54.73; H, 3.62; Br, 26.01; S, 10.44. Found: C, 54.58; H, 3.62; Br, 26.26; S, 10.32.

Kinetic Studies.—Acetic acid was purified for use as a solvent by the method described previously.[3] Spectroquality dioxane (Matheson Coleman and Bell) was dried by distilling from calcium hydride through a Widmer column. In preparing 80% aqueous dioxane 80 volumes of dioxane was mixed with 20 volumes of doubly distilled water at room temperature.

The kinetics of acetolysis of benzyl bromide, o- and p-carbophenoxybenzyl bromides, and p-thiolcarbophenoxybenzyl bromide were investigated through analysis of rate samples for excess acetate ion by titration with a standard solution of perchloric acid in acetic acid. The method has been described previously.[3] In studying acetolysis of o-thiolcarbophenoxybenzyl bromide an alternate method of analysis was employed, since the color of the mixture turns yellow as the reaction progresses. In this case 5-ml samples of the reaction mixtures were analyzed for bromide ion through extraction with water and titration of the aqueous extract by the Volhard procedure. Details of the method are given elsewhere.[1] The acetolysis rate constants for all bromides except for o-carbophenoxybenzyl and o-thiolcarbophenoxybenzyl bromides were calculated from the slopes of lines obtained by plotting values of log $[RBr]_t$ *vs.* time (eq 1). The

$$2.303 \log ([RBr]_i/[RBr]_t) = kt \qquad (1)$$

rate constants for the o-carbophenoxybenzyl and o-thiolcarbophenoxybenzyl bromides exhibit significant downward drifts during the course of the reactions. For these compounds the reported rate constants apply to early phases of the reactions. They were obtained by extrapolation of a plot of point-to-point rate constants (calculated using eq 1) *vs.* percentage reaction.

To study the rate of hydrolysis of o- and p-thiolcarbophenoxybenzyl bromides in 80% aqueous dioxane, a sample of the bromide was weighed into a volumetric flask, and the temperature of the flask was adjusted to the temperature of the rate run. Solvent, which had been equilibrated to this same temperature, was added to the mark. Samples (5 ml) were withdrawn from time to time and quenched in *ca.* 50 ml of chilled acetone. The solutions were analyzed for hydrogen ion by titrating with standard sodium hydroxide solution to the green end point of bromothymol blue indicator. Rate constants were calculated from the slopes of plots of log $[RBr]_t$ *vs.* time (eq 1).

Products of Acetolysis of o-Carbophenoxybenzyl and o-Thiolcarbophenoxybenzyl Bromides.—Small samples of the bromides in question were solvolyzed in 0.04 *M* sodium acetate in dry acetic acid under conditions comparable to those used in studying the reaction kinetics. After about 10 half-lives for reaction the acetic acid was removed under vacuum, and anhydrous ether was added to the residue. The undissolved salts were filtered off and the ether solution was concentrated by use of a rotary vacuum evaporator. The sole product obtained from o-carbophenoxybenzyl bromide was recrystallized from mixed hexanes and was identified as o-carbophenoxybenzyl acetate: mp 68.5–70°; nmr (CCl_4) δ 2.05 (s, 3, CH_3), 5.51 (s, 2, CH_2), 7.37 (m, 8, arom), and 8.17 ppm (m, 1, arom, ortho to C=O).

Anal. Calcd for $C_{16}H_{14}O_4$: C, 71.04; H, 5.23. Found: C, 71.09; H, 5.00.

The oily residue which resulted from the work-up of the acetolysis of o-thiolcarbophenoxybenzyl bromide proved to be a mixture of at least four products as shown by nmr analysis. The major product, comprising about 50% of the mixture, was isolated by alumina column chromatography and was identified as o-thiolcarbophenoxybenzyl acetate. Because of the small quantities available, however, it could not be completely purified: mp 86–89°; nmr (CCl_4) δ 2.05 (s, 3, CH_3), 5.50 (s, 2, CH_2), 7.78 (m, 8, arom), and 8.29 ppm (m, 1, arom, ortho to C=O).

Anal. Calcd for $C_{16}H_{14}O_3S$: C, 67.10; H, 4.94; S, 11.20. Found: C, 68.15; H, 5.16; S, 10.26.

Product of Hydrolysis of o-Thiolcarbophenoxybenzyl Bromide.—A small sample of the bromide was hydrolyzed in 80% aqueous dioxane at 65.0°. At the end of reaction time most of the solvent was evaporated under vacuum. The organic material was extracted into ether. Removal of the ether resulted in a solid residue. Recrystallization from mixed hexanes provided white crystals identified as phthalide: mp 72–73.5° (lit.[7] mp 73°).

(7) J. H. Gardner and C. A. Naylor, Jr., *Org. Syn.*, **16**, 71 (1936).

nmr (CCl_4, trace $CDCl_3$) δ 5.30 (s, 2, CH_2) and 7.68 ppm (m, 4, arom).

Results

The results of the rate runs on the several substituted benzyl bromides which have been investigated are summarized in Table I. The acetolyses of the o-COOC$_6$H$_5$

TABLE I
RATE CONSTANTS FOR SOLVOLYSIS OF BENZYL BROMIDES

Registry no.	X	$10^2[RBr]_i,$[a] mol/l.	10^2- [NaOAc], mol/l.	10^6k, sec^{-1}
		XC$_6$H$_4$CH$_2$Br in Acetic Acid at 85.0°		
100-39-0	H	1.37–2.30	2.00	1.23 ± 0.01[b]
	H	3.18	4.00	1.54[b]
34124-08-8	o-COOC$_6$H$_5$	1.17–2.06	2.00	4.76 ± 0.10[c]
	o-COOC$_6$H$_5$	2.45	4.00	5.80[c]
	o-COOC$_6$H$_5$	1.43	2.00[d]	1.44[c]
35092-35-4	p-COOC$_6$H$_5$	1.08–2.02	2.00	0.332 ± 0.012[b]
	p-COOC$_6$H$_5$	2.46	4.00	0.464[b]
	p-COOC$_6$H$_5$	1.51	2.00[d]	0.287[b]
35092-36-5	o-COSC$_6$H$_5$	1.08–1.54	2.00	173 ± 13[c]
	o-COSC$_6$H$_5$	1.93	4.00	173[c]
	o-COSC$_6$H$_5$	1.59	2.00[d]	43[c]
35129-59-0	p-COSC$_6$H$_5$	1.01–2.04	2.00	0.324 ± 0.007[b]
	p-COSC$_6$H$_5$	2.00	4.00	0.507[b]
	p-COSC$_6$H$_5$	1.05	2.00[d]	0.300[b]
		XC$_6$H$_4$CH$_2$Br in 80% Aqueous Dioxane at 65.0°		
	o-COSC$_6$H$_5$	1.41–2.62		120 ± 2[e]
	p-COSC$_6$H$_5$	1.13–1.90		14.8 ± 0.2

[a] In most instances, two or more runs were made in which $[RBr]_i$ was varied over the indicated range. [b] These values are based on the first 30–40% reaction. Rate constants are somewhat less beyond this point. [c] These values are based on data recorded in early phases of the runs. The reported rate constant at zero per cent reaction was obtained by extrapolation of a plot of point-to-point rate constants (eq 1) *vs.* percentage reaction. [d] $[NaBr]_i = 0.006$ *M*. [e] Included in the runs for which the average rate constant is reported is one in which the medium contained 2,6-lutidine (0.0214 mol/l., $[RBr]_i = 0.0141$ mol/l.). The value of the rate constant was not noticeably altered when lutidine was present.

and o-COSC$_6$H$_5$ derivatives are subject to marked common ion rate depression. Therefore the rate constants reported for these halides (based only on the initial phases of the runs) are to be regarded only as approximate, and if anything on the low side.

In Table II a summary is made of the k(ortho)/

TABLE II
RATE CONSTANT RATIOS FOR SOLVOLYSIS OF
o- AND p-XC$_6$H$_4$CH$_2$Br

| Medium X	k(ortho)/k(para) (Temp, °C)	
	80% Aqueous dioxane	Acetic acid
CH$_3$O		0.0017 (60)[a]
CH$_3$S		0.018 (60)[a]
OCOC$_6$H$_5$	0.21 (71.4); 0.20 (87.7)[b]	
COOCH$_3$	3.61 (71.4); 4.54 (87.7)[b]	
COOC$_6$H$_5$		14.3 (85.0)[c]
COSC$_6$H$_5$	8.11 (65.0)	534 (85.0)[c]

[a] From ref 5. The reported values are based on reactions of benzyl chlorides (rather than bromides) in acetic acid with $[RCl]_i = 0.05$ *M* and $[NaOAc]_i = 0.06$ *M*. [b] Values from ref 1. [c] Based on runs (Table I) in which $[NaOAc]_i = 0.0200$ *M*.

k(para) rate constant ratios for the substituted benzyl halides investigated in the present work and also for those obtained in earlier studies which are relevant for

comparative purposes. For reaction in 80% aqueous dioxane the rate constant ratios for the thiolcarbophenoxybenzyl bromides and the carbomethoxybenzyl bromides are comparable in magnitude. Though the ratios in both cases are not dramatically large, they are substantially greater than in cases in which the ortho substituent is nonparticipating, as for example when it is $-OCOC_6H_5$.

In acetic acid both the o-$COOC_6H_5$ and o-$COSC_6H_5$ substituted benzyl bromides solvolyze significantly faster than the corresponding para isomers. It is also noteworthy (Table I) that both ortho isomers, in contrast to the para analogs, are significantly more reactive in the acetolysis reactions than benzyl bromide itself (a fourfold difference in the case of o-$COOC_6H_5$ and *ca.* 140-fold for o-$COSC_6H_5$). On the other hand, the acetolysis rate constant at 60° for p-methoxybenzyl bromide is about 590 times that for the ortho isomer under the same conditions.[5] The relatively low reactivity of the latter is associated with steric hindrance to solvation at the reaction center by the o-methoxy substituent. If this value is used as an estimate of the magnitude of the rate constant ratio for acetolysis of substituted benzyl bromides when the ortho substituent is nonparticipating, it can be concluded that o-thiolcarbophenoxybenzyl bromide is *ca.* 310,000 times as reactive as it would be if the o-$COSC_6H_5$ group did not function as an internal nucleophile. It can be argued similarly that o-carbophenoxybenzyl bromide is *ca.* 8000 times as reactive as it would be if the o-$COOC_6H_5$ substituent were nonparticipating.

The fact that the o-$COSC_6H_5$ group is a substantially more effective participant than o-$COOC_6H_5$ is attributed to the differences in the capacities of oxygen and sulfur atoms to undergo positive polarization. Presumably forms such as I or II make very important contribution to structure at the transition state for acetolysis of o-thiolcarbophenoxybenzyl bromide. Significant common ion rate depression observed in the acetolyses of the o-$COSC_6H_5$ and o-$COOC_6H_5$ substituted benzyl

I   II
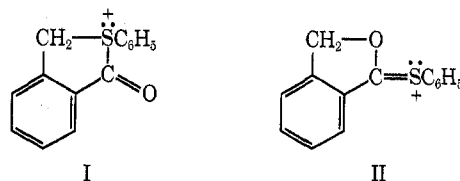
bromides (Table I) is considered to be a reflection of the stabilizing influence of the participating ortho substituents on structure at the transition state during the activation process[3] (either as shown in forms I and II, or through related involvement of oxygen atoms of the $COOC_6H_5$ group).

The fact that the ortho/para rate constant ratios for $-COSC_6H_5$ substituted benzyl bromides are much larger in acetic acid than in 80% aqueous dioxane brings to mind similar medium effects observed earlier in studies of the solvolyses of o- and p-NO_2 and o- and p-$COOC_6H_5$ substituted benzhydryl bromides.[3] It is also noteworthy that for reaction in acetic acid the k(ortho)/k(para) rate constant ratio for the $-COSC_6H_5$ substituted benzyl bromides is *ca.* 40 times larger than the ratio for the o- and p-carbophenoxybenzyl bromides. That is, in the solvolyses of the benzyl halides in question, as the medium becomes less suited to function as a solvating agent and as the nucleophilicity of the ortho substituent becomes stronger (through replacement of an O atom by S), the influence of the nucleophilic ortho substituent in stabilizing the developing positive charge at the reaction center through internal solvation is strikingly magnified.