3-methylcyclopentyl) propionic acid: b.p. 86–88° (5 mm.);  $n^{20}\mathrm{D}$  1.4638; infrared typical bands (liquid film), 1762 and 1160 cm. $^{-1}$ 

Anal. Caled. for C<sub>9</sub>H<sub>14</sub>O<sub>2</sub>: C, 70.10; H, 9.15. Found: C, 69.74; H, 9.20.

The residue of the distillation and the ether extracts gave 10.4 g. (19.4%) of trans-2-(2-hydroxy-3-methylcyclopentyl)propionic acid: m.p. 111-112°; infrared typical bands (Nujol mull), 3300 and 1705 cm.<sup>-1</sup>

Anal. Calcd. for C<sub>9</sub>H<sub>16</sub>O<sub>3</sub>: C, 62.76; H, 9.36. Found: C, 62.84; H, 9.38.

Lactonization of trans-2-(2-Hydroxy-3-methylcyclopentyl)propionic Acid.—When 3.0 g. of trans-2-(2-hydroxy-3-methylcyclopentyl)propionic acid were heated with 1 drop of concentrated sulfuric acid at 30 mm. in an oil bath at  $180-190^{\circ}$ , most of the material was distilled. The distillate was dried and 2.5 g. (96%) of the lactone of the *cis* acid, b.p. 92–93° (4 mm.),  $n^{20}$ D 1.4641, was obtained; infrared typical bands (liquid film), 1762 and 1160 cm.<sup>-1</sup>

Anal. Calcd. for  $C_9H_{14}O_2$ : C, 70.10; H, 9.15. Found: C, 70.04; H, 9.35.

Acknowledgment.—We thank Miss Kenko Ogawa of this laboratory for the elemental analyses reported here.

## Intramolecular Nucleophilic Participation. IV. The Hydrolysis Rates of Various ortho- and para-Substituted 1,1-Diphenylethyl Chlorides and Benzhydryl Chlorides and Bromides in Aqueous Acetone

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The relative reactivities of the *ortho* and *para* isomers of 1-carbophenoxyphenyl-1-phenylethyl chloride with respect to hydrolysis in aqueous acetone have been compared with those of the corresponding 1-phenyl-1-tolyl-ethyl chlorides and with those of the *o*- and *p*-carbophenoxybenzhydryl bromides and chlorides. It appears that the  $-COOC_8H_8$  group contributes much less extensively as a participating nucleophile in the reaction of 1-*o*-carbophenoxyphenyl-1-phenylethyl chloride than in the reactions of the *o*-carbophenoxybenzhydryl halides. The capacity of this group to promote the hydrolysis of *o*-carbophenoxybenzhydryl bromide seems to diminish as the water content of the medium is increased. The mechanistic implications of these results are discussed. Evidence is also presented that the NO<sub>2</sub> group does not participate extensively, if at all, in the hydrolysis of *o*-nitrobenzhydryl bromide.

It has been demonstrated that *o*-carbophenoxybenzhydryl bromide is hydrolyzed in aqueous acetone much more rapidly than is its *para* isomer.<sup>1</sup> The high reactivity of the *ortho* isomer is ascribed to its capacity to promote polarization of the carbon-halogen bond by releasing electrons to the p-orbital being vacated at the site of the displacement reaction (eq. 1). The evidence



for similar participation by the  $-\text{COOCH}_3$  group in the hydrolyses of *o*-carboethoxybenzyl and *o*-carbomethoxycumyl halides is negative.<sup>1,2</sup> It has been suggested, by way of explanation, that it is energetically critical for positive polarization of carbon at the reaction center of the benzyl and cumyl halides that the electron deficient p-orbital overlap the  $\pi$ -orbital of the ring. This constitutes an unfavorable geometric situation for participation by an *o*-COOCH<sub>3</sub> group.

The hydrolyses of benzhydryl halides in aqueous acetone are frequently discussed as examples of SN1-type solvolyses.<sup>3</sup> Clearly the carbon-halogen bonds must be substantially polarized, with solvent assistance, in the slow stages of these reactions. The slow step in the hydrolysis of *o*-carbophenoxybenzhydryl bromide is very likely a concerted process in which the exocyclic carbon loses bromide ion and simultaneously coordinates with the  $-COOC_6H_5$  group; that is, hydrolysis with *ortho*-substituent participation has some of the characteristics of an SN2-type reaction.

In this connection it has seemed of interest to determine whether changes in reactant structure and in medium polarity, which may be conducive to SN2 as opposed to SN1 displacement, have a favorable or unfavorable influence on the capacity of the o-carbophenoxy group to participate in benzhydryl halide hydrolysis. A comparison of the rates of solvolysis in aqueous acetone of the ortho and para isomers of 1-phenyl-1tolylethyl chloride and also of the o- and p-carbophenoxybenzhydryl chlorides has been made. An investigation of the effect of changes in the water content of aqueous acetone solvent mixtures on the ortho-para reactivity ratio for hydrolysis of the isomeric carbophenoxybenzhydryl bromides has also been conducted. As an incidental matter the hydrolysis rates of the oand *p*-nitrobenzhydryl bromides have been investigated to provide information concerning the nucleophilic character of the o-NO<sub>2</sub> group.

#### Experimental

1-p-Carbophenoxyphenyl-1-phenylethane.—The procedure of Szmant and Yoncoskie<sup>4</sup> was used in the preparation of 1,1-diphenylethane, b.p. 123–125° (6 mm.). This hydrocarbon was converted to 1-p-iodophenyl-1-phenylethane, b.p. 168–175° (0.5 mm.); the iodo compound was converted to 1-p-cyanophenyl-1-phenylethane, m.p. 50°, and the nitrile was hydrolyzed to provide a sample of p-1-phenethylbenzoic acid, m.p. 123°, by methods all of which have been described previously.<sup>4</sup> A 20-g. (0.088-mole) sample of the acid was heated with 10.5 g. (0.088 mole) of thionyl chloride for 1 hr., and 8.3 g. (0.088 mole)

<sup>(1)</sup> A. Singh, L. J. Andrews, and R. M. Keefer, J. Am. Chem. Soc., 84, 1179 (1962).

<sup>(2)</sup> J. L. Cotter, L. J. Andrews, and R. M. Keefer, J. Org. Chem., 28, 1917 (1963).

<sup>(3)</sup> See for example J. Hine, "Physical Organic Chemistry," 2nd Ed., McGraw-Hill Book Co., Inc., New York, N. Y., 1962.

of phenol was added. The mixture was again brought to  $100^{\circ}$  and then allowed to cool to room temperature. The crude product thus obtained (70% yield) was recrystallized from *n*-heptane to provide a sample of 1-*p*-carbophenoxyphenyl-1-phenylethane of m.p. 78°.

Anal. Caled. for  $C_{21}H_{18}O_2$ : C, 83.42; H, 5.99. Found: C, 83.52; H, 6.14.

1-o-Carbophenoxyphenyl-1-phenylethane.—A sample of the phenylmethylphthalide (m.p. 79°) prepared by the reaction of obenzoylbenzoic acid with methylmagnesium iodide was reduced with zinc dust in the presence of aqueous formic acid to o-1phenethylbenzoic acid<sup>5</sup> of m.p. 105°. A solution of 20 g. of this acid and 8.3 g. of phenol in 40 g. of pyridine was treated with 10.5 g. of thionyl chloride, and the mixture was heated at 100° for 1 hr. The pyridine was removed by distillation at reduced pressure, and the residue was dissolved in ether. This solution was washed successively with dilute hydrochloric acid and s0% yield by evaporation of the ether. It was recrystallized from petroleum ether (b.p. 60–80°) to provide a sample of 1-o-carbo-phenoxyphenyl-1-phenylethane of m.p. 40°.

Anal. Calcd. for  $C_{21}H_{18}O_2$ : C, 83.42; H, 5.99. Found: C, 83.01; H, 6.04.

1,1-Diphenylethyl Chloride (I).—The method of Schoepfle and Ryan<sup>6</sup> was used with slight modification in preparing this chloride from 1,1-diphenylethanol (Eastman Organic Chemicals). A suspension of 4 g. of the carbinol in 200 ml. of petroleum ether was cooled to 0°, treated with 20 g. of calcium chloride, and saturated with dry hydrogen chloride. The carbinol suspension disappeared as the mixture was gassed. The mixture was held at 0° overnight and then filtered to remove the drying agent. The petroleum ether was removed from the filtrate by evaporation at reduced pressure. The remaining 1,1-diphenylethyl chloride, which is known to decompose on distillation,<sup>6</sup> was not subjected to further purification procedures. A sample was analyzed for chlorine by titration for chloride ion liberated through solvolysis with 75% aqueous ethanol.

Anal. Caled. for C<sub>14</sub>H<sub>13</sub>Cl: Cl, 16.36. Found: Cl, 15.87. Preparation of 1,1-Diphenylethyl Chlorides by Photochlorination of the Corresponding 1,1-Diphenylethanes.—A photochlorination procedure similar to that used in synthesizing substituted cumyl chlorides from the corresponding cumenes<sup>2</sup> was employed. As is the case with the substituted cumyl chlorides<sup>2,7</sup> and 1,1diphenylethyl chloride itself, the ring-substituted 1,1-diphenylethyl chlorides are highly unstable with respect to loss of hydrogen chloride when efforts are made to purify them by distillation. In preparing a sample of 1,1-diphenylethyl chloride or of its p-carbophenoxy derivative (II) for use in rate work, about 1.0 g. of 1.1-diphenvlethane or 1-p-carbophenoxyphenyl-1-phenylethane was first cooled to 0° and then treated slowly with a measured volume (added from a microburet) of a 1.5 M solution of chlorine in carbon tetrachloride. During the addition process, which took about 1 hr., the reaction mixture was stirred magnetically and continuously irradiated with a 750-w. projection lamp. Approximately equimolar amounts of the halogen and the diphenylethane were used. When the addition was complete, the solvent was removed using a rotary film evaporator. The residual colorless oil, which undoubtedly contained traces of carbon tetrachloride as well as a substantial amount of unreacted diphenylethane, was used as a source of the diphenylethyl chloride

without further purification. The total chloride content of the oil (excluding that from residual traces of carbon tetrachloride) was determined by analysis for chloride liberated on hydrolysis of a weighed sample in aqueous acetone. In general, the oils obtained from the products of reaction of the *ortho-* as well as from the *para-substituted* and *-unsubstituted* diphenylethanes contained unreacted ester in substantial excess (5- to 13-fold on a mole basis) of the chloride.

The ortho isomer of 1-carbophenoxyphenyl-1-phenylethane does not react under the conditions described above which lead to photochlorination of the para isomer. Its low reactivity is considered to result from hindrance of the reaction center by the o-carbophenoxy group. The inert character of o-carbophenoxytriphenylmethane with respect to photobromination and oxidation has been similarly explained.<sup>8</sup> To convert them in part to the corresponding chloride (III), 1-g. samples of the ortho-substituted diphenylethane in 3 ml. of a 1.5 M solution of chlorine in carbon tetrachloride were gassed continuously for 1 hr. at 0° (with a total of about  $3 \times 10^{-2}$  moles of chlorine.) The resultant solutions were then concentrated as described in connection with the procedure for photochlorination of the para-substituted diphenylethane.

1-Phenyl-1-p-tolylethylene and 1-Phenyl-1-o-tolylethylene.— The ortho and para isomers of 1-phenyl-1-tolylethanol were prepared through reaction of 16.5-g. samples of acetophenone with the Grignard reagents prepared by the reactions of 3.7-g. samples of magnesium with 30 g. of the appropriate (o- and p-) iodotoluenes. After hydrolysis of the reaction products with ammonium chloride solution, the ether phases were concentrated to provide liquid samples of the crude alcohols. These could not be induced to crystallize nor could they be distilled without undergoing at least partial dehydration. They were converted to the 1-phenyl-1-tolylethylenes by repeated distillation (three or four times) under reduced pressure in the presence of iodine. The water produced during an individual distillation was recovered, along with the catalyst, in the first fraction which was collected. The final distillation provided 1-phenyl-1-o-tolyl-ethylene in 70% yield, b.p.  $158^\circ$  (22 mm.), and 1-phenyl-1-ptolylethylene in 80% yield, b.p. 166° (20.5 mm.). The para isomer solidified on cooling, m.p. (after recrystallization from petroleum ether) 105°.

Anal. Calcd. for  $C_{15}H_{14}$ : C, 92.73; H, 7.26. Found (ortho isomer): C, 92.11; H, 7.22. Found (para isomer): C, 92.67; H, 7.59.

Because it was surprisingly high melting in contrast to the ortho isomer, the possibility was considered that the para isomer might be dimeric in character. Its molecular weight in 90% aqueous ethanol was determined using a Mechrolab vapor pressure osmometer which was calibrated with aqueous ethanol solutions of biphenyl. The experimental molecular weight of 188  $\pm$  2 for the para isomer compares favorably with that (194) for monomeric C<sub>15</sub>H<sub>14</sub>.

The crude *para*-substituted ethylene may have been prepared previously by Cohen, Marshall, and Woodman<sup>9</sup> who distilled a liquid of b.p.  $175^{\circ}$  (28 mm.) from the hydrolyzed product of reaction of *p*-tolylmagnesium iodide and acetophenone; this liquid was actually described as phenyl *p*-tolylmethylcarbinol.

A sample of 1,1-diphenylethylene, b.p. 160° (28 mm.), lit.<sup>10</sup> b.p. 156° (25 mm.), was prepared by iodine-catalyzed dehydration of 1,1-diphenylethanol according to the general procedure described above.

Preparation of the 1,1-Diphenylethyl Chlorides and the 1-Phenyl-1-tolylethyl Chlorides .- Diarylalkene-contaminated samples of the unstable (with respect to HCl elimination) 1,1diphenylethyl chloride, 1-phenyl-1-o-tolyl chloride, and 1-phenyl-1-p-tolyl chloride were prepared for use in kinetic experiments by gassing 0.2-g. samples of the appropriate diarylethylenes in 10 ml. of benzene with dry hydrogen chloride for 2-hr. periods. The solution temperatures were held at 0° during the hydrogen chloride additions. The solvent was removed from the resultant mixtures by evaporation under reduced pressure. The residues, which were viscous oils, contained approximately 10% of the theoretical quantity of hydrochlorination product. These gradually evolved hydrogen chloride on prolonged evaporation. In one instance the product of hydrochlorination of 1-phenyl-1p-tolylethylene was reconverted to the starting ethylene, m.p. 105°, when it was held under vacuum for a long period of time. The chloride contents of these residues were established through analyses for the total hydrogen chloride liberated (after completion of the hydrolysis reaction) when weighed samples were dissolved in aqueous acetone.

Benzhydryl bromide (IV) and o- (V) and p-carbophenoxybenzhydryl bromide (VI) were prepared by photobromination of diphenylmethane and of the phenyl esters of o- and p-benzylbenzoic acids by the methods outlined previously.<sup>1</sup>

<sup>(5) (</sup>a) E. Bergmann, J. Org. Chem., 4, 1 (1939). (b) H. Heymann and L. Trowbridge, J. Am. Chem. Soc., 72, 84 (1950). (c) The reduction with formic acid was patterned after a procedure used in reducing 3,3-diphenylphthalide [R. L. Letsinger, J. D. Jamison, and A. S. Hussey, J. Org. Chem., 26, 97 (1961)].

<sup>(6)</sup> C. S. Schoepfle and J. D. Ryan, J. Am. Chem. Soc., 54, 3692 (1932).
(7) H. C. Brown, J. D. Brady, M. Grayson, and W. H. Bonner, *ibid.*, 79, 1897 (1957).

<sup>(8)</sup> R. E. Lovins and L. J. Andrews, J. Org. Chem., 29, 487 (1964).

<sup>(9)</sup> J. B. Cohen, J. Marshall, and H. E. Woodman, J. Chem. Soc., 107, 887 (1915).

<sup>(10)</sup> C. F. H. Allen and S. Converse, "Organic Syntheses," Coll. Vol. I, 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1941, p. 226.

o- (VII) and p-Carbophenoxybenzhydryl Chloride (VIII).—In a typical preparation a solution of 6.2 g. (0.022 mole) of phenyl o-benzylbenzoate<sup>1</sup> in 20 ml. of carbon tetrachloride was cooled to 0°, and 22 ml. of a solution of 1.01 *M* chlorine in carbon tetrachloride was added dropwise with stirring. The mixture was irradiated during the addition with a 750-w. projection lamp. The solvent was removed using a rotary film evaporator and the residue (o-carbophenoxybenzhydryl chloride) was crystallized from ligroin, yielding 4.3 g. (62%), m.p. 83°. The para isomer was prepared from phenyl p-benzylbenzoate in 67% yield by this same procedure, m.p. 87-88°.

Anal. Calcd. for  $C_{20}H_{15}ClO_2$ : C, 74.41; H, 4.65; Cl, 11.00. Found (ortho isomer): C, 74.86; H, 4.75; Cl, 10.70. Found (para isomer): C, 74.76; H, 4.75; Cl, 10.84.

**Benzhydryl chloride** (IX) was prepared from benzhydrol and anhydrous hydrogen chloride,<sup>11</sup> b.p. 144–145° (4 mm.).

p-Nitrobenzhydrol.—A sample of p-nitrobenzophenone, m.p. 138°, was prepared by the Friedel-Crafts reaction of p-nitrobenzoyl chloride and benzene according to the method of Schroeter.<sup>12</sup> A solution of diborane  $(2 M \text{ in BH}_3)$  was prepared according to the directions of Zweifel and Brown.<sup>13</sup> A 35-ml. sample of this solution was added slowly to a mixture of 15 g. (0.070 mole) of p-nitrobenzophenone and 50 ml. of freshly distilled tetrahydrofuran. The reaction flask was immersed in an ice bath during the addition. The mixture was then stirred overnight at room temperature under an atmosphere of nitrogen. Water was added to destroy excess hydride. Anhydrous sodium carbonate was added to the resultant mixture, and the tetrahydrofuran layer was separated and concentrated under reduced pressure. The oily residue crystallized from aqueous ethanol solution after standing 4 days to provide 8.2 g. of p-nitrobenzhydrol, m.p. 76-77° (lit.<sup>14</sup> m.p. 76-78°). The authors are indebted to Professor George Zweifel for his invaluable assistance in connection with the reduction of the ketone.

*p*-Nitrobenzhydryl bromide (X) was prepared in 72% yield through the gassing of a benzene solution of *p*-nitrobenzhydrol with hydrogen bromide, m.p.  $31-32^{\circ}$  (lit.<sup>15</sup> m.p.,  $32-34^{\circ}$ ).

The procedure was much the same as that reported previously<sup>1</sup> for converting o- and p-methylbenzhydrols to the corresponding bromides.

o-Nitrobenzhydryl Bromide (XI).-All attempts to obtain a pure sample of o-nitrobenzhydryl bromide failed. When onitrobenzhydrol<sup>16</sup> was treated with hydrogen bromide in benzene, an oil separated which contained halogen but which could not be crystallized or distilled. In the procedure finally chosen in preparing an impure sample of the bromide for rate work, o-nitrodiphenylmethane was first prepared by the Friedel-Crafts reaction of o-nitrobenzyl chloride (Aldrich Chemical Co.) and benzene<sup>17</sup> and purified by distillation with superheated steam.<sup>18</sup> A 6.0-g. (0.028-mole) sample of this product was dissolved in 40 ml. of carbon tetrachloride. A 7.4-g. (0.042-mole) sample of Nbromosuccinimide was added along with a small amount of benzoyl peroxide, and the mixture was refluxed for 24 hr. The mixture was then chilled, and the succinimide was removed by filtration. The filtrate was washed with dilute aqueous sodium hydroxide and water and dried over sodium sulfate. After removal of the solvent, a dark brown oil remained which could not be induced to crystallize and which underwent decomposition when distillation was attempted. The o-nitrobenzhydryl bromide content of this oil (which was used directly in the rate work) was obtained by analyzing for the hydrogen bromide liberated when weighed samples were heated with aqueous acetone.

The Kinetic Studies.—The rate runs were generally initiated by dissolving a weighed sample of the organic halide in aqueous acetone to provide solutions of known volume. The solvent mixtures later described as (100 - x)% aqueous acetone were prepared by mixing 100 - x volumes of purified acetone with x volumes of water. Samples of known volume of the reaction mixture were removed from time to time and analyzed for halide ion liberated through the hydrolysis reaction. Other details of

(15) A. Ilecito, A. Fava, U. Mazzucato, and O. Rossetto, J. Am. Chem. Soc., 83, 2729 (1961).

TABLE I

# RATE CONSTANTS FOR HYDROLYSIS OF THE BENZHYDRYL

AND 1,1-DIPHENTLETHYL HALIDES				
		T	Range <sup>a</sup> of [RBr] <sub>i</sub>	1052
x	Compd	°C	or [RCI]i,	$10^{\circ}k_{\rm B}$ ,
XC.H	CCCH V	он. С.н. у	$\frac{1}{2} = \frac{1}{2} = \frac{1}$	aug Agotono
TT AC611	40(0113)( T	05 1	$\sim 100\%$ Aqui	Ang L op
	I T	20.1	0.0200	$420 \pm 83$
H	1	11,4	0.0235	90.9
H H	I	11.4	0.0353	88.70
H H DOOD H	1	11.4	0.0572	$104^{\circ}$
0-COOC6H5	111	25.1	0.0187	$7.50 \pm 0.15$
p-COOC <sub>6</sub> H <sub>5</sub>	11	25.1	0.0232	$5.29 \pm 0.13$
o-COOC <sub>6</sub> H <sub>5</sub>	111	11.4	0.012-0.022	$1.93 \pm 0.02$
p-COOC <sub>6</sub> H <sub>5</sub>	11	11.4	0.0247	$1.40 \pm 0.03$
XC6H	$I_4CH(C_6]$	H₅)Br i	n 80% Aqueou	s Acetone
H	IV	30.0	0.063-0.173	$166 \pm 1.3$
$o-\mathrm{COOC}_6\mathrm{H}_5$	V	30.0	0.035-0.038	$81.9 \pm 0.5$
p-COOC <sub>6</sub> H <sub>5</sub>	VI	30.0	0.047 - 0.059	$2.47 \pm 0.12$
$o-\mathrm{COOC_6H_5}$	V	45.0	0.035 - 0.143	$369 \pm 3$
p-COOC <sub>6</sub> H <sub>5</sub>	VI	45.0	0.044 - 0.118	$11.56 \pm 0.17$
$o-\mathrm{NO}_2$	XI	30.0	0.060-0.100	$0.36 \pm 0.03$
p-NO <sub>2</sub>	Х	30.0	0.032 - 0.040	$0.56 \pm 0.03$
$o-\mathrm{NO}_2$	$\mathbf{XI}$	45.0	0.063 - 0.153	$2.41 \pm 0.02$
p-NO <sub>2</sub>	Х	45.0	0.047 - 0.154	$2.42 \pm 0.10$
$\mathrm{XC}_{6}$	H <sub>4</sub> CH(C	<sub>6</sub> H <sub>5</sub> )Br	in 90% Aqueo	us Acetone
o-COOC <sub>6</sub> H <sub>5</sub>	V	25.0	0.020-0.091	$14.4 \pm 0.2^{d}$
p-COOC <sub>6</sub> H5	VI	25.0	0.020-0.090	$0.167 \pm 0.003^{d}$
o-COOC <sub>6</sub> H <sub>5</sub>	V	45.0	0.018-0.078	$97 \pm 4^d$
p-COOC <sub>6</sub> H <sub>5</sub>	VI	<b>45</b> .0	0.022-0.040	$1.64 \pm 0.03^{d}$
o-NO <sub>2</sub>	XI	45.0	0.043	0.43
$p-NO_2$	Х	45.0	0.035	0.34
XCeH	LCH(C <sub>6</sub> ]	H₅)Br i	n 95% Aqueou	s Acetone
0-COOC.H.	v	30 0	0 043-0 048	7 7
n-COOC <sub>6</sub> H <sub>5</sub>	vi	30 0	0 079	0.053
a-COOCeHe	v	45 0	0 047-0 070	$32.9 \pm 0.2$
p-COOC <sub>4</sub> H <sub>5</sub>	VI	45.0	0.034-0.094	$0.28 \pm 0.01$
XC.H.	CCHAC	L'H')C	1  in  80% Aque	ous Acetone
• COOC H.		10.2	0.011	$20.5 \pm 0.5$
~ COOC H	111 11	10.2	0.011	$20.3 \pm 0.3$
<i>p</i> -COOC <sub>6</sub> II5	11	94.7	0.040	$15.7 \pm 0.5$ 75.0 ± 1.5
		24.7	0.014	$73.0 \pm 1.5$
<i>p</i> -00006115		44.7 T.)01.5	0.000 - 0007 A	/0.1 ± 1.0
AU6F	14CH(C6		n $80\%$ Aqueou	s Acetone
H		30 0	0.074-0.130	$11.92 \pm 0.06$
H	1X	45.0	0.079-0.281	$47.9 \pm 0.2$
o-COOC <sub>6</sub> H <sub>5</sub>	V 11	30.0	0.045-0.075	$1.59 \pm 0.18$
p-COOC <sub>6</sub> H <sub>5</sub>	VIII	30.0	0.071 - 0.136	$0.083 \pm 0.004$
o-COOC6H₅	117	45.0	0.040-0.083	$9.07 \pm 0.53$
p-COOC <sub>6</sub> H <sub>5</sub>	VIII	45.0	0.051 - 0.100	$0.63 \pm 0.01$

<sup>a</sup> With many of the halides several runs were made in which  $[RCI]_i$  or  $[RBr]_i$  was varied over the indicated range. The reported  $k_s$  values are averages of the values for these runs. <sup>b</sup> In the preceding runs on 1,1-diphenylethyl chloride or its carbophenoxy derivatives the halide which was used was prepared by partial photochlorination of the corresponding diphenylethane in carbon tetrachloride. The crude product was used in rate work, without purification, after evaporating the bulk of the solvent. In this run a relatively pure sample of the organic chloride, prepared from the carbinol and hydrogen chloride, was used. <sup>c</sup> A relatively pure sample of 1,1-diphenylethyl chloride was used. Carbon tetrachloride (0.15 M) and 1,1-diphenylethane (0.15 M) were added to determine the effects of small amounts of these contaminants on  $k_s$ . <sup>d</sup> From A. Singh, L. J. Andrews, and R. M. Keefer, J. Am. Chem. Soc., **84**, 1179 (1962).

the kinetic experiments, including the purification of the acetone used in the solvent mixtures, are given in earlier publications.<sup>1,2</sup> The solvolysis rates constants  $k_s$ , as defined in eq. 2, were calculated from the slopes of the linear plots of log [RX] vs. t, where [RX] is the molar concentration of organic halide at time t.

<sup>(11)</sup> A. M. Ward, J. Chem. Soc., 2288 (1927).

<sup>(12)</sup> G. Schroeter, Ber., 42, 3360 (1909),

<sup>(13)</sup> G. Zweifel and H. C. Brown, Org. Reactions, 13, 31 (1964).

<sup>(14)</sup> R. T. Puckowski and W. A. Ross, J. Chem. Soc., 3555 (1959).

<sup>(16)</sup> Prepared by the method of D. H. Hey and R. D. Mulley, J. Chem. Soc., 2276 (1952).

<sup>(17)</sup> R. Geigy and W. Königs, Ber., 18, 2402 (1885).

<sup>(18)</sup> S. Gabriel and R. Stelzner, ibid., 29, 1300 (1896).

The runs generally were followed at least to 70% of completion. In most cases two or three runs, in which the initial organic halide concentrations were varied by a factor of two or more, were made to evaluate the rate constant for a particular halide in a particular solvent mixture.

As has been discussed above, pure samples of the o- and pcarbophenoxy derivatives of 1,1-diphenylethyl chloride could not be prepared. Rate samples containing these chlorides were prepared from the products of partial photochlorination of the corresponding diphenylethanes. To check the validity of  $k_{\rm s}$ values obtained under such circumstances, the rate constant for hydrolysis of a sample of 1,1-diphenylethyl chloride prepared by partial photochlorination of 1,1-diphenylethane was compared with that obtained using a sample of the chloride prepared from 1,1-diphenylethanol and hydrogen chloride. The constants thus obtained were in reasonably good agreement with each other and with that for a run in which the pure chloride sample was adulterated with contaminants (carbon tetrachloride and 1,1-diphenylethane) which were present in the photochlorinated material (see Table I).

For reasons described above the relative hydrolysis rates of the 1-phenyl-1-tolylethyl chlorides were determined using impure samples of the chlorides prepared by addition of hydrogen chloride to the corresponding 1-phenyl-1-tolylethylenes. As a check on the validity of this procedure a run was also made with an impure sample of 1,1-diphenylethyl chloride similarly prepared from the corresponding substituted ethylene and hydrogen chloride. The half-life for hydrolysis of the chloride in this sample was closely similar to that for a run under comparable conditions in which organic chloride prepared from the carbinol and hydrogen chloride was used (see Tables I and II).

#### TABLE II

RELATIVE RATES OF SOLVOLYSIS IN AQUEOUS ACETONE OF BENZHYDRYL AND 1,1-DIPHENYLETHYL HALIDES

		Temp.		Relative
X	Compd.	°C,	% acetone	$rate^{a}$
$XC_6H_4C(CH_3)(C_6H_5)Cl$				
н	I	11.4	90	68
Н	I	25.1	90	81
o-COOC <sub>6</sub> H <sub>5</sub>	III	11.4	90	1.38
o-COOC <sub>6</sub> H <sub>5</sub>	III	25.1	90	1.42
$o-\mathrm{COOC_6H_5}$	III	10.2	80	1.04
$o-\mathrm{COOC}_6\mathrm{H}_5$	III	24.7	80	1.03
	XC	$C_6H_4CH(C_6)$	H <sub>5</sub> )Br	
o-COOC <sub>6</sub> H <sub>5</sub>	v	30.0	95	145
o-COOC <sub>6</sub> H <sub>5</sub>	$\mathbf{V}$	45.0	95	118
o-COOC <sub>6</sub> H <sub>5</sub>	$\mathbf{V}$	25.0	90	86
$o-\mathrm{COOC}_6\mathrm{H}_5$	V	45.0	90	59
o-NO <sub>5</sub>	XI	45.0	90	0.26
p-NO <sub>5</sub>	X	<b>45</b> .0	90	0.21
H	IV	30.0	80	67
o-COOC <sub>6</sub> H <sub>5</sub>	'v	30.0	80	33
o-COOC <sub>6</sub> H <sub>5</sub>	$\mathbf{V}$	45.0	80	32
$o-\mathrm{NO}_2$	XI	30.0	80	0.15
$o-\mathrm{NO}_2$	XI	45.0	80	0.21
p-NO <sub>2</sub>	X	30.0	80	0.23
p-NO <sub>2</sub>	Х	45.0	80	0.21
H 0-COOC <sub>6</sub> H <sub>5</sub> 0-COOC <sub>6</sub> H <sub>5</sub> 0-NO <sub>2</sub> 0-NO <sub>2</sub> p-NO <sub>2</sub> p-NO <sub>2</sub>	IV V V XI XI X X X	$   \begin{array}{r}     45.0 \\     30.0 \\     45.0 \\     30.0 \\     45.0 \\     30.0 \\     45.0 \\     45.0 \\   \end{array} $	80 80 80 80 80 80 80	67 33 32 0.15 0.21 0.23 0.21

<sup>a</sup> Solvolysis rate relative to that for X = p-COOC<sub>6</sub>H<sub>5</sub> at the same temperature.

#### Results

The  $k_s$  values for hydrolysis of the various benzhydryl and 1,1-diphenylethyl halides are summarized in Table I and a summary of relative reactivities is given in Table II. The ratios of the rate constants of the ortho and para isomers of 1-o-carboxyphenyl-1-phenylethyl chloride  $[C_6H_5OOCC_6H_4C(CH_3)(C_6H_5)Cl]$  for reaction both in 80 and 90% aqueous acetone are close to unity. The ortho isomer of 1-phenyl-1-tolylethyl chloride  $[CH_3C_6H_4C(CH_3)(C_6H_5)Cl]$  is, however, appreciably less reactive than the para isomer. In fact the reactivity of the latter compound is sufficiently high so that it has not been possible to make a detailed study of the kinetics of its hydrolysis. The  $k_{\rm s}(ortho)/k_{\rm s}(para)$ ratio based on the observed (Table III) half-lives for the reactions of the 1-phenyl-1-tolylethyl chlorides in 90% aqueous acetone at 10.2° falls between the limits 0.013– 0.05. The corresponding ratio for the o- and p-carbophenoxydiphenylethyl chlorides (III and II, 1.38 at 11.4°) is of the order of 30 to 100 times as large as that for the methyl-substituted diphenylethyl chlorides. This difference in reactivity ratios may be fully or in part the result of participation by the  $-\text{COOC}_6\text{H}_5$  group in the reaction of the o-carbophenoxy compound.

#### TABLE III

RELATIVE HYDROLYSIS RATES OF THE ortho AND para ISOMERS OF 1-PHENYL-1-TOLYLETHYL CHLORIDE IN 90% AQUEOUS ACETONE (10.2°)

		/
х	[RCl] <sub>i</sub> , mole/l.	$t_{1/2},^{c}$ sec.
	$XC_6H_4C(CH_3)(C_6H_5)Cl$	
$o$ - $CH_{3}^{a}$	0.0032	$1200 \pm 240$
$p$ - $\mathrm{CH}_{3^{a}}$	0.0020	$60 > t_{1/2} > 15$
$p ext{-} ext{CH}_3{}^b$	0.0320	$60 > t_{1/2} > 15$
$\mathrm{H}^{a}$	0.0037	$780 \pm 120$

<sup>a</sup> The sample of organic chloride which was used was prepared from the corresponding diphenylethylene as described in the Experimental section. <sup>b</sup> The sample of organic chloride was prepared by gassing a sample of the corresponding crude carbinol in petroleum ether with gaseous HCl. The ether solution was dried with calcium chloride and the crude product remaining after evaporation of the solvent was used in the rate run. About 30% of the carbinol was converted to chloride as a result of the treatment with hydrogen chloride. <sup>c</sup> Half-life for the hydrolysis reaction. The half-life for the third run of Table I, in which the chlorides was prepared from 1,1-diphenylethanol and HCl, is 778 sec. (11.4°).

Using the data<sup>1</sup> reported previously for reactions in 90% aqueous acetone, it has been estimated that at  $9.5^{\circ}$ the  $k_{\rm s}(ortho)/k_{\rm s}(para)$  ratio for the hydrolysis of the carbophenoxybenzhydryl bromides (V and VI) is about 1000 times as large as that for the o- and p-methylbenzhydryl bromides. Even if a reasonable allowance is made for the fact that the  $k_s(ortho)/k_s(para)$  ratio apparently is somewhat less when chlorine rather than bromine is the departing halogen (cf. the ratios for the carbophenoxybenzhydryl halides in 80% aqueous acetone in Table I), it seems safe to conclude that o-carbophenoxy group participation occurs much more extensively in the reactions of the benzhydryl halides than in those of the diphenylethyl halides. A direct comparison of the reactivities of either the bromides or of the chlorides derived from the diphenylmethanes and the 1,1-diphenylethanes cannot be made conveniently because of vast differences in their solvolysis rates.

In the light of the results discussed above it might appear that as the structure of the organic halide is altered to favor polarization of the carbon-halogen bond, the nucleophilic *ortho* substituent plays a diminishingly important role in inducing rupture of that bond. By way of explanation it might be argued that because of differences in the susceptibilities of secondary and tertiary halides to bimolecular (SN2) attack, the *o*-carbophenoxy group would function more effectively as an internal nucleophile in the reactions of the benzhydryl halides than in those of the diphenylethyl halides. In predicting the relative effectiveness of a participating *ortho* substituent in promoting the hydrolysis of benzhydryl halides and structurally related compounds, the ease of nucleophilic attack on the carbons at the reaction centers is not, however, the only factor to be considered.<sup>19</sup> If this criterion is invoked, it is predicted that o-carbophenoxybenzyl bromide (III) should hydrolyze much more readily than its para isomer II, and this is contrary to fact.<sup>1</sup> Apparently, a subtle balance in those structural characteristics of the reacting halide which are conducive to SN1 and to SN2 displacements is required for maximum ortho-substituent participation. Insofar as hydrolysis in aqueous acetone is concerned, that balance is better achieved with benzhydryl halides than with benzvl or 1.1-diphenvlethvl halides. It is possible that the lack of evidence for the involvement of the ortho substituent in the hydrolysis of o-carbomethoxycumyl chloride, which has been explained on other grounds,<sup>2</sup> may reflect to some degree the resistance of the tertiary halide to attack by the internal nucleophile.

The Medium Effect on  $k_s(ortho)/k_s(para)$ .—The ratio of rate constants for hydrolysis of the *o*- and *p*-carbophenoxybenzhydryl bromides at 30.0° drops by a factor of over 4 as the solvent is changed from 95 to 80% aqueous acetone. A change of similar magnitude is observed for the ratios of rate constants at 45°. Presumably the fractions of these reactions which proceed with *ortho* participation diminish as the solvent becomes increasingly better constituted to support ionization of the carbon-bromine bond. It seems likely that the positive charge which develops on activation is more dispersed when hydrolysis of the benzhydryl halide proceeds with (eq. 1) than without (eq. 3) *ortho*-substituent assistance.



This conclusion is based on the assumption that the extent of positive-charge delocalization through involvement of the  $\pi$ -orbitals of the aromatic nuclei is about the same for either process. The change to the more polar solvent is, therefore, expected to favor the latter process (eq. 3) more than the former<sup>20</sup> (eq. 1) and, as is observed experimentally, to result in a substantial reduction in the  $k_s(ortho)/k_s(para)$  ratio for the carbophenoxybenzhydryl bromides. There is a smaller, but nonetheless noticeable, decrease (with increasing solvent polarity) in the rate constant ratio for the 1carbophenoxyphenyl-1-phenylethyl chlorides. It is possible that this decrease may also be a reflection of the

(19) It has been shown that in displacement reactions of saturated systems of the type  $% \left[ \left( {{{\mathbf{x}}_{i}} \right)_{i \in I} } \right]$ 



which may proceed at least in part with participation of -SA as a neighboring group



 $\alpha$ -methyl or phenyl groups actually lower the driving force due to the neighboring group [S. Winstein and E. Grunwald, J. Am. Chem. Soc., **70**, 812 (1948)].

(20) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p. 346. capacity, which is admittedly limited in intensity, of the carbophenoxy group to participate in the hydrolysis of the *ortho* chloride.

The Nitro Group as an Internal Nucleophile.—In the above discussion the reactivities of the o- and p-carbophenoxy-substituted compounds have been related to those of the analogous o- and p-methyl-substituted organic halides in assigning an order of magnitude to the contribution of the o-COOC<sub>6</sub>H<sub>5</sub> group to reactivity. Actually halides bearing substituent groups which, like  $-COOC_6H_5$ , are electron withdrawing but which do not function as internal nucleophiles would be more appropriate reference compounds than the methyl analogs. In this connection a comparison of the hvdrolysis rates of the o- and p-nitrobenzhydryl bromides (XI and X) has been undertaken.  $k_s(ortho)/k_s(para)$ ratios are 1.00 and 1.26, respectively, for reaction at  $45^{\circ}$  in 80 and 90% aqueous acetone. It seems reasonable that a substituent as sizable as o-NO<sub>2</sub> should interfere with solvation at the sight of positive-charge development in the activation process for solvolysis<sup>21</sup> sufficiently so that, in the absence of ortho-substituent participation, the  $k_s(ortho)/k_s(para)$  ratio for these bromides should be appreciably less than unity. It might thus be concluded that the o-NO<sub>2</sub> substituent does indeed serve as a nucleophile in the benzhydryl bromide reaction, although its influence on reactivity is much less than that of the o-COOC<sub>6</sub>H<sub>5</sub> group under the same conditions. Further comment on this point is made below in the section on thermodynamic constants. It has been suggested, on the basis of the results of a study of the effects of changes in solvent composition on activation energy that the o-nitro group may serve as an intramolecular solvating agent in the reaction of onitrobenzyl chloride in aqueous ethanol.<sup>22</sup> In this

## TABLE IV THE ENERGIES AND ENTROPIES OF ACTIVATION FOR

Hydrolysis	$\mathbf{OF}$	THE	Halides	
	$\mathbf{F}$			

	$E_{8}$		
X	kcal./mole	$-\Delta S^*$ , e.u.	
XC <sub>6</sub> H <sub>4</sub> C(CH <sub>3</sub> )(C <sub>6</sub> H <sub>5</sub> )Cl in 80% Aqueous Acetone			
$o-\mathrm{COOC}_6\mathrm{H}_5$	$15.0\pm0.4$	$24.6 \pm 1.3$	
p-COOC <sub>6</sub> H <sub>5</sub>	$15.1 \pm 0.3$	$24.3 \pm 1.3$	
$XC_6H_4C(CH_3)(C_6H_5)Cl$ in 90% Aqueous Acetone			
Н	$18.3 \pm 2.6$	$10.1 \pm 8.7$	
o-COOC <sub>6</sub> H <sub>5</sub>	$16.7 \pm 0.3$	$23.5 \pm 1.0$	
$p ext{-} ext{COOC}_6 ext{H}_5$	$16.4 \pm 0.4$	$25.2 \pm 1.3$	
XC6H4CH(C6H5)Br in 80% Aqueous Acetone			
o-COOC <sub>6</sub> H <sub>5</sub>	$19.2 \pm 0.2$	$11.3 \pm 0.7$	
p-COOC <sub>6</sub> H <sub>5</sub>	$19.7 \pm 0.7$	$16.6 \pm 2.3$	
$o\text{-NO}_2$	$24.3 \pm 1.1$	$5.3 \pm 3.6$	
p-NO <sub>2</sub>	$18.7 \pm 0.9$	$22.9\pm3.0$	
${ m XC_6H_4CH(C_6H_5)Br}$ in 95% Aqueous Acetone <sup>a</sup>			
$o-\mathrm{COOC}_6\mathrm{H}_5$	$18.5 \pm 0.6$	$18.3 \pm 1.9$	
$p extsf{-}\mathrm{COOC}_6\mathrm{H}_5$	$21.3 \pm 0.9$	$19.0 \pm 3.0$	
$\rm XC_6H_4CH(C_6H_5)Cl$ in $80\%$ Aqueous Acetone			
H	$17.8 \pm 0.2$	$19.8 \pm 0.6$	
o-COOC <sub>6</sub> H <sub>5</sub>	$22.2 \pm 1.7$	$9.3 \pm 5.6$	
p-COOC <sub>6</sub> H <sub>5</sub>	$25.9 \pm 0.7$	$2.9 \pm 2.3$	

<sup>a</sup> For reaction in 90% aqueous acetone values of  $E_a = 17.4 \pm 0.4$  and  $21.2 \pm 0.2$ , and  $\Delta S^* = 18.8 \pm 1.3$  and  $16.1 \pm 0.7$  have been reported.<sup>1</sup>

<sup>(21)</sup> For pertinent data relating to the effect of o-Cl and o-CH<sub>3</sub> groups on the rate of ethanolysis of benzhydryl chloride, see (a) J. F. Norris and C. Banta, J. Am. Chem. Soc., **50**, 1804 (1928); (b) J. F. Norris and J. T. Blake, *ibid.*, **50**, 1808 (1928).

<sup>(22)</sup> J. B. Hyne and R. Wills, *ibid.*, **85**, 3650 (1963).

case, however, the *ortho* substituent makes a contribution to reactivity which is minor at most.

Thermodynamic Constants.—Activation energies and entropies have been calculated for those hydrolyses for which the appropriate data (Table I) are available. These are summarized in Table IV. In making comparisons of these thermodynamic constants the limits of error which are reported, and which in some instances are large, can be overlooked only at the risk of over-interpretation of the data. The  $E_a$  and  $\Delta S^*$ values for the isomeric 1-carbophenoxyphenyl-1-phenylethyl chlorides are closely similar, a fact which is considered to support the conclusion that the  $-\text{COOC}_6\text{H}_5$ group does not contribute extensively as a nucleophile to the reaction of the ortho isomer.

Benzhydryl bromides which bear nonparticipating ortho substituents (e.g.,  $-\text{OCOC}_6\text{H}_5)^1$  have substantially higher  $E_a$  values for hydrolysis than do their para isomers. This difference is associated with hindrance by the ortho substituent to solvation in the transition state. The  $E_a$  values for o-carbophenoxybenzyhydryl bromide are generally less than those for the para isomer. The differential appears to be considerably smaller for reactions in 80% aqueous acetone than for reactions in media of lower water content, which are more conducive to

ortho-substituent participation. The differential in  $E_a$  values for the carbophenoxybenzhydryl chlorides appears to be significantly larger than that for the bromides even if the limits of error are taken into account.

It is difficult to explain many of the observed differences in entropies of activation for the reactions of ortho and para isomers. Losses of entropy which result directly from involvement of the ortho substituent may be more than offset by reductions in entropy losses which, in the absence of participation, are associated with the solvation of the center of positive polarization in the transition state. The fact that the activation energy for hydrolysis of *o*-nitrobenzhydryl bromide is considerably larger than that for the para isomer can be offered as evidence that the o-NO<sub>2</sub> substituent does not make an important contribution to reactivity as a participating nucleophile. The relatively low value of  $-\Delta S^*$  for the ortho isomer appears to counterbalance the high  $E_{\rm a}$  value sufficiently so that the reactivities (Table I) of the ortho and para isomers are about the same.

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### Nucleophilic Displacement Reactions of 2-Amino-4-alkylthiopteridines<sup>1-3</sup>

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The synthesis of 2-amino-4-thiopteridine and of 2-amino-4-alkylthiopteridines is described. The latter compounds undergo nucleophilic attack in the 4-position by hydroxide, hydrosulfide, ammonia, hydrazine, and hydroxylamine under mild conditions. The differences in the susceptibility to nucleophilic displacement of 4-alkylthiopteridines and 6-alkylthiopurines are discussed.

The widespread clinical use, as antileukemic agents,<sup>6</sup> of folic acid analogs in which the hydroxy group in the 4-position of the pteridine ring was replaced by an amino group, raised interest in new approaches to the introduction of other substituents into the 4-position of pteridines. Nucleophilic displacement reactions with 2-amino-4-alkylthiopteridines appear to represent a convenient method for accomplishing this purpose.

While several groups of workers have described the synthesis of 6,7-disubstituted 2-amino-4-thiopteridines,<sup>7-10</sup> no 2-amino-4-thiopteridines or 2-amino-4-alkylthiopteridines unsubstituted in the pyrazine ring have been reported.

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(5) To whom requests for reprints should be addressed.

(6) S. Farber, et al., New Engl. J. Med., 238, 787 (1948).

(7) E. C. Taylor, R. B. Garland, and C. F. Howell, J. Am. Chem. Soc., 78, 210 (1956).

(8) M. J. Fahrenbach and K. H. Collins, U. S. Patent 2,756,230 (July 24, 1956).

These compounds were obtained by the following synthetic sequence.



<sup>(9)</sup> M. J. Fahrenbach and K. H. Collins, U. S. Patent 2,767,181 (Oct. 15, 1956).

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<sup>(10)</sup> E. J. Modest, S. Chatterjee, S. A. Lemlein, and D. M. Brun, Abstracts, 138th National Meeting of the American Chemical Society, New York, N. Y., Sept., 1960, p. 4-0.