Intramolecular Nucleophilic Participation. VI. Forced Carbomethoxy Group Participation in the Solvolysis of 1-(2,6-Dicarbomethoxyphenyl)ethyl Bromide

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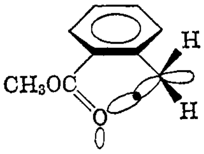
Abstract: A comparative study has been made of the rates of hydrolysis of the 2,4- and 2,6-dichloro- and 2,4- and 2,6-dicarbomethoxy derivatives of benzyl bromide, the 1-(2,4- and 2,6-dichlorophenyl)ethyl bromides, and the 1-(2,4- and 2,6-dicarbomethoxyphenyl)ethyl bromides in 80 vol % aqueous dioxane. The four disubstituted benzyl bromides react at comparable rates. At 70.7° the 2,4-dichloro derivative of 1-phenylethyl bromide is about one-half as reactive as its 2,4-dicarbomethoxy analog, but 1-(2,6-dichlorophenyl)ethyl bromide is only $^1/_{120}$ as reactive as its 2,6-dicarbomethoxy analog. On the basis of an analysis of the electronic and steric influences of the ring substituents (Cl and $COOCH_3$) on the reactivities of these organic bromides, the high solvolysis rate of 1-(2,6-dicarbomethoxyphenyl)ethyl bromide is attributed to a geometric situation which forces intramolecular nucleophilic participation of the carbomethoxy groups in the displacement process.

The rates of solvolysis of the *o*-carbophenoxy[1] and *o*-nitro[2] derivatives of benzhydryl bromide are substantially greater than those of the *para* isomers, presumably because the *ortho* substituents participate as internal nucleophiles in the breaking of the carbon–bromine bond. The *ortho* and *para* isomers of the carbomethoxybenzyl bromides[1] are, however, solvolyzed at comparable rates as are also the *o*- and *p*-nitrobenzyl tosylates[2] and chlorides.[3] In accounting for the fact that *ortho* substituent involvement of the type under consideration is not extensive in the reactions of the benzyl halides, two possible conformational arrangements, a and b, for the activated complex for the solvolysis of *o*-carbomethoxybenzyl bromide have been discussed.[1,2,4] It is assumed that the carbon atom at the reaction center (the α carbon of the substituted toluene) is appreciably positively polarized in the activated complex, and in a and b this carbon is depicted as fully trigonal in character for illustrative purposes.[5] It is further assumed that the carbomethoxy group lies in the ring plane. Apparently the activated complex resembles conformer b rather than a; that is, it is stabilized through delocalization of ring π electrons rather than by electron release from the carbomethoxy group.



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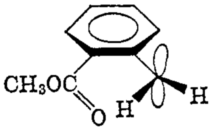

b

The possibility has been considered that if sufficiently bulky substituents are introduced in place of hydrogen in the vicinity of the reaction center of the *o*-carbomethoxybenzyl bromide molecule, either at the vacant *ortho* position or at the α carbon (or in both places), participation of the *o*-carbomethoxy group in solvolytic processes may be forced. This matter has been explored experimentally by comparing the rates of hydrolysis of the 2,4- and 2,6-dichlorobenzyl bromides, the 2,4- and 2,6-dicarbomethoxybenzyl bromides, the 1-(2,4- and 2,6-dichlorophenyl)ethyl bromides, and the 1-(2,4- and 2,6-dicarbomethoxyphenyl)ethyl bromides in 80% aqueous dioxane.

Experimental Section

The Dichlorotoluenes. Samples of the 2,4- and 2,6-dichlorotoluenes, obtained from Eastman Organic Chemicals, were used without further purification.

1-Ethyl-2,4-dichlorobenzene. A mixture of 24.0 g (0.43 mol) of potassium hydroxide in 180 ml of degassed diethylene glycol, 50 g (0.24 mol) of 2′,4′-dichloroacetophenone and 29 ml of 85% hydrazine hydrate was refluxed for 3 hr. About 25 ml of material was removed from the mixture by distillation. The distillate was retained, and the remaining reaction mixture was refluxed for 6 hr. The distillate and cooled reaction mixture were extracted with ether several times, and the combined extracts were dried and concentrated by distillation. The oily residue was distilled under reduced pressure to provide 27.4 g (64% yield) of 1-ethyl-2,4-dichlorobenzene, bp 68.5° (1.5 mm). An analytically pure sample was not prepared. The nmr spectrum of the product (neat) showed a triplet centered at τ 9.07 and a quartet at τ 7.60 (characteristic of the ethyl group) as well as a multiplet at τ 2.90–3.30 (aromatic H). The peak ratios were 3:2:3.

1-Ethyl-2,6-dichlorobenzene. A Grignard reagent prepared from 6.3 g of magnesium and an ether solution of 61.4 g of 2,6-dichlorobenzyl bromide was treated dropwise with 63 g of dimethyl sulfate. The resultant mixture was stirred 18 hr and then hydrolyzed with iced dilute hydrochloric acid solution. The ether solution of the product was concentrated to about 20% of the original volume, and the concentrate was refluxed with an equal volume of 10% sodium hydroxide solution for 6 hr to destroy dimethyl sulfate. The dried ether phase was further concentrated using a rotary evaporator. The by-product (2,2′,6,6′-tetrachlorodibenzyl), mp 152–154°, precipitated when the oily residue was cooled. The solid was filtered, and the filtrate was distilled at a pressure of 2.5 mm to provide two 10-ml fractions (bp 73–75 and 75–77°) and a 2-ml fraction (bp 77–78°). It was established on the basis

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[1] A. Singh, L. J. Andrews, and R. M. Keefer, *J. Am. Chem. Soc.*, **84**, 1179 (1962).

[2] A. D. Mease, M. J. Strauss, I. Horman, L. J. Andrews, and R. M. Keefer, *ibid.*, **90**, 1797 (1968).

[3] J. B. Hyne and R. Wills, *ibid.*, **85**, 3650 (1963).

[4] J. L. Cotter, L. J. Andrews, and R. M. Keefer, *J. Org. Chem.*, **28**, 1917 (1963).

[5] It is quite generally recognized that benzyl halide solvolysis is a type of reaction which lies mechanistically on the borderline between an SN1 and SN2 process. See, for example, for pertinent information and other references: (a) B. Bensley and G. Kohnstam, *J. Chem. Soc.*, 4747 (1957); (b) G. Kohnstam and P. R. Robinson, *ibid.*, 4970 (1957); (c) C. R. Cowie, H. J. M. Fitches, and G. Kohnstam, *ibid.*, 1585 (1963); (d) J. B. Hyne and R. E. Robertson, *Can. J. Chem.*, **34**, 863 (1956). For purposes of the present discussion it is sufficient to adopt the point of view that at the transition state in reactions of this kind the organic halide has developed significant ionic character.

of their nmr spectra that these fractions consisted largely of 1-ethyl-2,6-dichlorobenzene contaminated with 2,6-dichlorotoluene (approximately 20, 15, and 5 mole %, respectively, in the three fractions). The formation of the toluene derivative could not be prevented even though the normal precautions to exclude traces of water were taken in the preparation and further reaction of the Grignard reagent. The ratio of ethylbenzene derivative to toluene derivative in the product was calculated from the peak areas of the triplet (CH_3 of the ethyl group) and singlet (CH_3 of the toluene derivative) appearing at high field in the nmr spectrum of the mixture. The crude mixture was used in subsequent synthetic processes and, where it was most feasible to do so, the mixtures of products derived from toluene and ethylbenzene were separated by vapor phase chromatography.

In later stages of the research it was found that a product free of the toluene derivative could readily be prepared by the catalytic reduction of 2,6-dichlorostyrene (Aldrich Chemical Co.) according to the general procedure described by Fieser.[6] In this way 8.2 g (52% yield) of 1-ethyl-2,6-dichlorobenzene, bp 130° (70 mm), was obtained from 15.0 g of the dichlorostyrene. The nmr spectrum of this product neat showed a triplet centered at τ 9.01, a quartet at 7.27, and a multiplet at 2.8–3.5 (relative peak areas 3:2:3). An analytically pure sample was not prepared.

2,4- and 2,6-Dicyanotoluenes. The various dichlorobenzene derivatives employed in this investigation were converted to the corresponding dinitriles by reaction with cuprous cyanide at high temperature.[7] In a typical preparation, 48.3 g (0.30 mol) of 2,6-dichlorotoluene, 53.8 g (0.60 mol) of cuprous cyanide, 0.1 g of cupric sulfate, 0.5 ml of benzonitrile, and 25 ml of dry pyridine were heated under a nitrogen atmosphere for 3 days, at which time the temperature of the mixture was 240°. Heating was continued, and the mixture was stirred for 15 hr. The hot material was cooled to 115° and poured into a rapidly stirred solution of 200 ml of concentrated ammonium hydroxide and 50 ml of water. The resultant mixture was stirred vigorously with several batches of an equal volume mixture of benzene and ether. The decanted organic phases were combined (600-ml total volume) and were washed successively with dilute ammonium hydroxide, water, and saturated sodium chloride solution. The solvent was removed and the residue was crystallized from absolute ethanol. After recrystallization 11.1 g (26% yield) of 2,6-dicyanotoluene was obtained as colorless needles, mp 134–136° (lit.[7] mp 134–135°).

Through the reaction of 48.3 g of 2,4-dichlorotoluene with cuprous cyanide 10.6 g (25% yield) of crude 2,4-dicyanotoluene, mp 139–141° (lit.[8] mp 144–145°) was obtained.

1-Ethyl-2,4- and 1-Ethyl-2,6-dicyanobenzene. The crude product of reaction of 1-ethyl-2,4-dichlorobenzene with cuprous cyanide was a yellow oil. The nmr spectrum of the sample suggested that it was contaminated with 2-ethyl-5-chlorobenzonitrile and 3-chloro-4-ethylbenzonitrile. The oil was used without purification, and the undesired contaminants were removed in a subsequent step leading to the preparation of 1-(2,4-dicarbomethoxyphenyl)ethyl bromide (see below).

Crude 1-ethyl-2,6-dicyanobenzene was prepared by way of the reaction of an 85:15 mole % mixture of 1-ethyl-2,6-dichlorobenzene and 2,6-dichlorotoluene with cuprous cyanide. From 43.9 g of the starting material 15.3 g of dinitrile (39% yield calculated on the assumption that the starting material and product were uncontaminated with toluene derivatives) was obtained, mp 85–86°.

Anal. Calcd for $C_{10}H_8N_2$: C, 76.90; H, 5.16; N, 17.94. Found: C, 76.53; H, 4.96; N, 18.20.

The nmr spectrum of this product in carbon tetrachloride showed peaks characteristic of the ethyl group centered at τ 8.61 (triplet) and 6.89 (quartet). A singlet peak from the methyl group of the dicyanotoluene contaminant appeared at τ 7.23. From the relative peak areas it was estimated that the extent of contamination was about 10 mole %.

Dimethyl 2- and 4-Methylisophthalates. A mixture of 12.4 g of 2,6-dicyanotoluene and 150 ml of 10% sodium hydroxide solution was refluxed for 5 hr. On acidification of the resultant solution 15.5 g (98% yield) of 2-methylisophthalic acid was obtained, mp 242–244° (lit.[9] mp 228–230°). The same procedure was used in converting 10.5 g of 2,4-dicyanotoluene to 9.5 g (71% yield) of 4-methylisophthalic acid, mp >300° dec (lit.[8] mp 320–330° subl).

Through esterification of 15.5 g of 2-methylisophthalic acid in excess methanol with sulfuric acid as catalyst, 11.3 g (57% yield) of the corresponding dimethyl methylisophthalate was obtained, mp 56.5–58° (lit.[10] mp 56–57°). Similarly 9.5 g of 4-methylisophthalic acid gave 6.3 g (72% yield) of dimethyl 4-methylisophthalate, mp 79° (lit.[8] mp 79–80°).

Dimethyl 2-Ethylisophthalate. Crude 2-ethylisophthalic acid was prepared by hydrolyzing the impure 1-ethyl-2,6-dicyanobenzene by the procedure outlined above. From 11 g of the dinitrile, 13.4 g (98% yield assuming that the starting material contained no dicyanotoluene) of the acid was obtained, mp 225–235°. A 6.5-g sample of the crude acid, which was about 10 mole % 2-methylisophthalic acid, was converted to the diacid chloride using thionyl chloride. The reaction of the diacid chloride with methanol provided 4.2 g of crude dimethyl 2-ethylisophthalate, the nmr spectrum of which indicated that it contained about 7 mole % of dimethyl 2-methylisophthalate. The mixture was separated by preparative vapor phase chromatography using a 10 ft × 3/8 in. column packed with 25% S.F.-96-50 on Chromosorb W, 60–80 mesh. A sample of the 3.2 g of dimethyl 2-ethylisophthalate which was recovered was reinjected on this same column and only one peak was observed. Although this material was not analytically pure (combustion), the nmr spectrum showed it to be free of the methyl isophthalate. The spectrum (neat) displayed a triplet, a singlet, a quartet, and a multiplet, centered respectively at τ 9.17, 6.58, 7.25, 2.5–3.5 with peak areas in the ratio 3:6:2:3.

Dimethyl 4-Ethylisophthalate. The crude dinitrile obtained from 1-ethyl-2,4-dichlorobenzene and cuprous cyanide was hydrolyzed, by using 10% sodium hydroxide, to furnish 4.0 g of the corresponding crude diacid. The nmr spectrum of this material in pyridine indicated that it was substantially contaminated, presumably with monochloromonocarboxy derivatives of ethylbenzene. The diacid was converted with thionyl chloride to the crude diacid chloride, and this was converted to diester by refluxing it with methanol. The crude product was purified by vapor phase chromatography using the same column employed in the separation of dimethyl 2-ethylisophthalate. In this way 1.62 g (6.1% yield based on 1-ethyl-2,4-dichlorobenzene used as starting material) was obtained, mp 20°.

Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 65.02; H, 6.13.

The nmr spectrum (neat) of the diester showed a triplet, a quartet, a singlet, and a multiplet centered respectively at τ 4.12, 7.35, 6.39, and 1.8–3.2, with peak areas in the ratio 3:2:6:3.

The Dichloro- and Dicarbomethoxybenzyl Bromides and the α-(Dichlorophenyl)- and α-(Dicarbomethoxyphenyl)ethyl Bromides. With the exception of dimethyl 4-methylisophthalate, which was treated with molecular bromine, the dichloro and dicarbomethoxy derivatives of toluene and ethylbenzene were subjected to benzylic bromination by reaction with N-bromosuccinimide. The yields, physical properties, elemental analyses, and salient features of the nmr spectra of the various bromides are summarized in Table I.

The reaction of dimethyl 2-methylisophthalate with N-bromosuccinimide is typical of the general procedure. A mixture of 9.1 g (0.051 mol) of the brominating agent, 0.01 g of benzoyl peroxide, and 11.4 g (0.049 mol) of the ester in a small volume of dry carbon tetrachloride was refluxed for 2 hr.[11] The succinimide remaining after completion of the reaction was filtered, and the filtrate was concentrated under vacuum to remove the solvent. In this case the residue, which was crystalline, was recrystallized from carbon tetrachloride to yield 14 g of 2,6-dicarbomethoxybenzyl bromide as colorless needles.

In preparing 2,4-dicarbomethoxybenzyl bromide a solution of 3.9 g (0.017 mol) of dimethyl 4-methylisophthalate in 50 ml of carbon tetrachloride was treated dropwise with 2.72 g (0.017 mol) of bromine in 20 ml of the same solvent. The mixture was stirred and irradiated with a 750-W tungsten lamp during the addition. When the bromine was consumed, the solvent was removed under vacuum, and the residue was recrystallized from a 1:1 mixture of hexane and carbon tetrachloride to provide 3.0 g of the white crystalline product.

The Rate Studies. The aqueous dioxane used as the medium in investigating the kinetics of hydrolysis of the substituted benzyl

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(6) L. F. Fieser, "Organic Experiments," D. C. Heath and Co., Boston, Mass., 1965, p 86.

(7) W. S. Lindsay, P. Stokes, L. G. Humber, and V. Boekelheide, *J. Am. Chem. Soc.*, **83**, 943 (1961).

(8) W. Borsche, *Ann.*, **386**, 368 (1912).

(9) C. Graebe and R. Bossel, *ibid.*, **290**, 213 (1896).

(10) R. C. Elderfield and S. L. Wythe, *J. Org. Chem.*, **19**, 683 (1954).

(11) L. Chauffe, L. J. Andrews, and R. M. Keefer, *ibid.*, **31**, 3758 (1966).

Table I. Characterization of the Bromides[a]

Compd	R_2	Yield,[b] %	Mp (bp (mm)), °C	Calcd, %			Found, %			Nmr absorption,[c] τ
				C	H	Br	C	H	Br	
The Benzyl Bromides ($R_2C_6H_3CH_2Br$)										
I	2,6-$(COOCH_3)_2$	82	94–94.5	46.03	3.83	27.84	45.96	3.79	28.02	s, 4.7 (2 H) s, 6.2 (6 H) m, 2.0–3.0 (3 H)
II	2,4-$(COOCH_3)_2$	61	79.5–80	46.03	3.83	27.84	46.01	3.84	27.92	s, 5.05 (2 H) s, 6.05 (3 H) s, 6.10 (3 H) m, 1.6–2.4 (3 H)
III	2,6-Cl_2	70	55[d]	35.04	2.10	33.31	35.08	2.26	33.20	. . .
IV	2,4-Cl_2	64	(109–112 (2.5–3))[e]	35.04	2.10	33.31	34.92	2.22	33.20	s, 5.83 (2 H) m, 3.0–3.4 (3 H)
The 1-Phenylethyl Bromides ($R_2C_6H_3CH(Br)CH_3$)										
V	2,6-$(COOCH_3)_2$	56	57.5–58.5	47.86	4.35	26.54	48.01	4.29	26.68	d, 8.70 (3 H) s, 6.43 (6 H) q, 4.70 (1 H) m, 2.3–3.3 (3 H)
VI	2,4-$(COOCH_3)_2$	23	*f*	47.86	4.35	26.54	47.81	4.10	26.72	d, 8.13 (3 H) s, 6.22 (3 H) s, 6.23 (3 H) q, 3.80 (1 H) m, 1.7–2.5 (3 H)
VII	2,6-Cl_2	42	(93 (0.6))	37.83	2.78	27.92	37.65	2.79	27.78	d, 7.73 (3 H) q, 3.85 (1 H) m, 2.5–3.0 (3 H)
VIII	2,4-Cl_2	48	(90 (0.5))[g]	37.83	2.78	27.92	37.95	2.57	27.98	d, 8.12 (3 H) q, 4.54 (1 H) m, 2.3–3.1 (3 H)

[a] Except as noted these compounds have not been prepared previously. [b] Based on the toluene or ethylbenzene derivative which was brominated. [c] The letters s, d, q, and m represent singlet, doublet, quartet, and multiplet, respectively. The relative numbers of hydrogen atoms corresponding to each absorption peak, as determined from peak areas, are given in parentheses. [d] F. Kronke and K. E. Ellegast, *Ann.*, **600**, 176 (1956), report mp 55°. [e] E. L. Eliel, T. N. Ferdinand, and M. C. Hermann, *J. Org. Chem.*, **19**, 1693 (1954), report bp 126–133° (8 mm). [f] A liquid which was not distilled because of the susceptibility of *o*-carbomethoxy derivatives of benzyl halides to thermal decomposition (see ref 1). [g] E. B. Evans, E. E. Mabbott, and E. E. Turner, *J. Chem. Soc.*, 1159 (1927), report bp 154° (37 mm).

and 1-phenylethyl bromides was prepared by mixing 20 volumes of doubly distilled water with 80 volumes of purified[1] dioxane at room temperature. Solvolysis rate constants which are reported are defined by eq 1, in which $(RBr)_i$ and $(RBr)_t$ represent the organic bromide concentrations initially and at time t. They were calculated from the slopes of plots of values of log (RBr) *vs.* t.

$$2.303 \log (RBr)_i/(RBr)_t = k_s t \qquad (1)$$

Generally rate measurements were continued until the reactions were at least two-thirds complete.

Two methods of analysis of rate samples were used. In the first of these, samples of the reaction mixtures were removed from time to time and analyzed for liberated bromide ion by the Volhard method.[1]

The alternate procedure was similar to the nmr method used in a previous investigation.[12] As a further check on the validity of the nmr method, it has been established by separate measurement that the difference in the position of the water peak in 80 vol % aqueous dioxane and that in an internal capillary filled with water is linearly related to the hydrogen bromide concentration from 0 to 0.50 *M* HBr. For rate runs at 70.7 and 85.7°, 0.5-ml samples of the reaction mixture at various times were rapidly chilled to quench the reaction. Later they were brought to the temperature of the Varian 60-Mc nmr spectrometer and the water-filled capillary reference (held vertically by Teflon spacers) was inserted. The spectra were then recorded and the rate constants[12] were evaluated from the slope of the log $(\delta_t - \delta_\infty)$ *vs.* time plots.

Products of Solvolysis of the Dicarbomethoxy Derivatives of Benzyl and 1-Phenylethyl Bromides. Small samples of the substituted benzyl and 1-phenylethyl bromides were hydrolyzed in 80% aqueous dioxane under conditions comparable to those used in studying the reaction kinetics. After at least eight half-lives had elapsed, the solvent was removed from each mixture by distillation at reduced pressure at temperatures below 60°. The residues were extracted with ether, and the dried ether extracts were concentrated to dryness. The remaining solids were recrystallized from petroleum ether (bp 30–60°). The products are identified and their properties summarized in Table II.

Spectra. Infrared spectra which are reported were recorded with a Beckman IR-8 spectrophotometer. The nmr spectra were recorded with a Varian 60-Mc instrument, and tetramethylsilane was used as the reference standard.

Results

In comparing the relative solvolysis rates of the 2,4- and 2,6-dicarbomethoxybenzyl bromides (II and I) and of the 1-(2,4- and 2,6-dicarbomethoxyphenyl)ethyl bromides (VI and V) with the matter of *o*-carbomethoxy group participation in mind, some knowledge of the effects of 2,4 and 2,6 substituents other than carbomethoxy on the reactivities of the parent halides is required. The 2,4- and 2,6-dichlorobenzyl (IV and III) and 1-(2,4- and 2,6-dichlorophenyl)ethyl bromides (VIII and VII) have been selected as the appropriate model compounds, since chlorine is not constituted to function effectively as a participating group but, like carbomethoxy, is an electron-withdrawing ring substituent so far as its influence on reactions at aromatic side chains is concerned. Rate constants for hydrolysis of the several organic bromides in 80 vol % aqueous dioxane are summarized in Table III.

The ratio of the solvolysis rate constants for the 2,6- and 2,4-dichlorobenzyl bromides is slightly less than unity (Table I) and of the same order of magnitude as the rate constant ratios generally observed for solvolysis of the *ortho* and *para* isomers of monosubstituted benzyl halides.[1,13,14] Evidently, the combined

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(12) See ref 2.

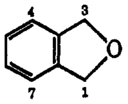
(13) (a) S. C. J. Olivier, *Rec. Trav. Chim.*, **49**, 697 (1930); (b) S. C. J. Olivier, *ibid.*, **53**, 869 (1934).

(14) J. C. Charlton and E. D. Hughes, *J. Chem. Soc.*, 850 (1956).

Table II. Hydrolysis Products of $BrCH_2C_6H_3(COOCH_3)_2$ and $CH_3CH(Br)C_6H_3(COOCH_3)_2$

Reactant	Product[a]	Mp, °C	Infrared bands,[b] cm^{-1}	Nmr absorption,[c] τ	Calcd, % C	Calcd, % H	Found, % C	Found, % H
I	1-Oxo-4-phthalancarboxylic acid	246[d]	3500 (OH) 1745 (C=O) 1680 (acid C=O)	s, 5.0[e]	60.68	3.39	60.76	3.64
II	1-Oxo-6-phthalancarboxylic acid	226	3600 (OH) 1755 (C=O) 1680 (acid C=O)	s, 5.38[e]	60.68	3.39	60.40	3.60
V	1-Oxo-3-methyl-4-phthalancarboxylic acid, methyl ester	95–98	1760 (C=O) 1718 (ester C=O)	d, 8.5 (3 H) s, 6.15 (3 H) q, 4.22 (1 H) m, 1.72–2.8 (3 H)	64.07	4.89	64.35	4.62
VI	1-Oxo-3-methyl-6-phthalancarboxylic acid, methyl ester[f]	97–104	3500 (OH) 1760 (C=O) 1750 (ester C=O)	d, 8.28 s, 6.0 q, 4.4 m, 1.5–2.5	...	...	...	...

[a] Product names are based on the phthalan ring structure



[b] Solid samples in KBr pellets were used. [c] See footnote c, Table I; solvent for esters, CCl_4; for acids, pyridine. [d] E. Wenkert, D. Johnston, and K. Dave, *J. Org. Chem.*, **29**, 2534 (1964), report mp 246–247°. [e] The aromatic region was obscured by solvent. [f] A mixture which probably contained 1-oxo-3-methyl-6-phthalancarboxylic acid.

Table III. Rate Constants for Hydrolysis of the Bromides in 80% Aqueous Dioxane

Compd	R_2	Temp, °C	Range[a] of $[ArCH_2Br]_i$, *M*	10^5k_s,[b] sec^{-1}	$k_s(2,6)/k_s(2,4)$
		The Benzyl Bromides ($R_2C_6H_3CH_2Br$)			
I	2,6-$(COOCH_3)_2$	70.7	0.016–0.083	0.539 ± 0.03	0.55
II	2,4-$(COOCH_3)_2$	70.7	0.011–0.077	0.971 ± 0.03	
I	2,6-$(COOCH_3)_2$	45.4	0.020–0.170	0.045 ± 0.001	0.58
II	2,4-$(COOCH_3)_2$	45.4	0.022–0.045	0.078 ± 0.02	
III	2,6-Cl_2	70.7	0.052–0.135	0.420 ± 0.002	0.78
IV	2,4-Cl_2	70.7	0.078–0.178	0.541 ± 0.03	
III	2,6-Cl_2	85.7	0.026–0.101	1.39 ± 0.035	0.66
IV	2,4-Cl_2	85.7	0.034–0.126	2.09 ± 0.138	
		The 1-Phenylethyl Bromides ($R_2C_6H_3CH(Br)CH_3$)			
V	2,6-$(COOCH_3)_2$	70.7	0.107–0.446	14.0 ± 0.71	4.47
VI	2,4-$(COOCH_3)_2$	70.7	0.082	3.13	
V	2,6-$(COOCH_3)_2$	45.4	0.083–0.343	0.958 ± 0.006	3.20
VI	2,4-$(COOCH_3)_2$	45.4	0.119	0.299	
VII	2,6-Cl_2	70.7	0.034–0.090	0.116 ± 0.009	0.062
VIII	2,4-Cl_2	70.7	0.035–0.050	1.88 ± 0.218	
VII	2,6-Cl_2	85.7	0.045–0.150	0.409 ± 0.016	0.054
VIII	2,4-Cl_2	85.7	0.049–0.157	7.57 ± 0.35	

[a] Three runs at different initial concentrations were made where sufficient material was available. [b] Thermodynamic constants have been calculated from k_s values reported at two temperatures for each compound. Values of E_a in kilocalories and $\Delta S^{\ddagger}$ in entropy units (the latter in parentheses) for the substituted benzyl bromides I–IV are respectively 21.4 ± 0.5 (22.8 ± 1.4), 21.7 ± 2.7 (23.6 ± 7.8), 19.6 ± 0.4 (28.5 ± 1.2), and 22.1 ± 1.4 (20.6 ± 4.1). The corresponding constants for the substituted α-phenylethyl bromides V–VIII are respectively 23.1 ± 0.4 (11.3 ± 1.3), 20.2 (22.7), 20.6 ± 1.5 (28.1 ± 4.3), and 22.8 ± 0.5 (16.2 ± 1.5).

bulk of the α-hydrogen atoms and *o*-chlorines is not sufficient to cause steric problems pronounced enough to be reflected in the rate of solvolysis of the 2,6-disubstituted compound.

The situation is, however, much different for the 1-(2,4- and 2,6-dichlorophenyl)ethyl bromides. The 2,6 isomer is only of the order of $^1/_{16}$ as reactive as the 2,4. In the activated complex for the reaction of these dichlorophenylethyl halides the bonds to the trigonal α carbon should enter the ring plane to provide for maximum stabilization through π-electron delocalization. In the case of the 2,6 isomer, this is not possible without serious steric compression resulting from interaction of the α-CH_3 and *o*-Cl substituents. As can be illustrated with a molecular model, there is a strain-free conformation which permits such a coplanar arrangement during the reaction of 1-(2,4-dichlorophenylethyl) bromide. A similar explanation has been proposed previously by Charlton and Hughes[14] in accounting for the fact that the ratio of solvolysis rates (aqueous ethanol) of the 1-(2,6- and 2,4-dimethylphenyl)ethyl chlorides is much less than that for the 2,6- and 2,4-dimethylbenzyl chlorides.[15]

It is likely that solvation of the activated complex for the hydrolysis of 1-(2,6-dichlorophenyl)ethyl bromide is subject to severe steric hindrance,[16] and this too should reflect unfavorably on reactivity of the halide. Even though the hydrolysis of the 2,4 isomer may be somewhat retarded for the same reason, the

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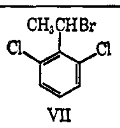
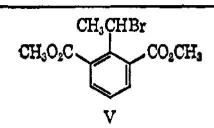
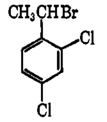
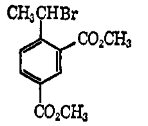
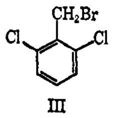
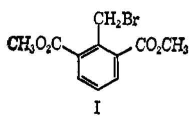
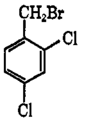
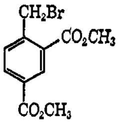
(15) See also J. Baddeley, J. Chadwick, and H. T. Taylor, *J. Chem. Soc.*, 2405 (1954).

(16) S. Winstein and B. K. Morse, *J. Am. Chem. Soc.*, **74**, 1133 (1952).

magnitude of the effect certainly should be much less than when the phenylethyl halide has two substituents, rather than one, *ortho* to the reaction site.

The ratio of the hydrolysis rate constants, $k_s(2,6)/k_s(2,4)$, for the dicarbomethoxybenzyl bromides (I and II) is of the order of 0.6 in the 45–70° region, close to that for the corresponding dichlorobenzyl bromides (III and IV). In fact all four compounds have similar solvolysis rate constants, as is illustrated in Table IV in which the reactivities of the various benzyl and phenylethyl bromides are compared with that of 1-(2,6-dichlorophenyl)ethyl bromide (VII). It appears that the electronic effects of the 2,4- and 2,6-dichloro and -dicarbomethoxy substituents, as exerted through the aromatic nucleus, are much the same. Also, it seems that steric interactions between o-CO_2CH_3 groups and α hydrogens are low enough in intensity during rate-determining processes to have little, if any, influence on the reactivities of the dicarbomethoxybenzyl halides.

Table IV. Relative Solvolysis Rate Constants of 2,4- and 2,6-Disubstituted Benzyl and 1-Phenylethyl Bromides (80% Aqueous Dioxane; 70.7°)

Compound	k_s[a]	Compound	k_s[a]
 VII	1	 V	120
 VIII	16.2	 VI	26.9
 III	3.6	 I	4.6
 IV	4.7	 II	8.4

[a] Relative.

In sharp contrast to 1-(2,6-dichlorophenyl)ethyl bromide (VII), which as noted above is much less reactive than its 2,4 isomer VIII, 1-(2,6-dicarbomethoxyphenyl)ethyl bromide (V) hydrolyzes at a rate about four times that for its 2,4 isomer VI. In the light of the comparative electronic effects of carbomethoxy and chlorine substituents and of the relative steric consequences on reactivity of 2,4 and 2,6 disubstitution as discussed above, V must therefore be classed as an abnormally reactive bromide. The magnitude of this abnormality is readily apparent in the figures presented in Table IV. With the exception of V, each of the dicarbomethoxy-substituted bromides (VI, I, and II) differs in reactivity from its corresponding dichloro-substituted bromide (VIII, III, and IV, respectively) by a factor of no more than 2. Yet V hydrolyzes 120 times more readily than its chlorine analog VII.

Like the two chlorine atoms in VII the two o-carbomethoxy groups must prevent a coplanar orientation of the ring plane and the bonds to trigonal carbon in the activation process for hydrolysis of V. Barring other influences of the carbomethoxy groups, it should be anticipated that V should be much less instead of much more reactive than its isomer VI and comparable in reactivity to VII. Since, however, the trigonal carbon is almost certainly twisted out of the ring plane in the activated complex for reaction of V, its vacant p orbital is probably favorably oriented as in conformer a of the introductory section to accept electrons from both o-$COOCH_3$ groups.[17] It appears, therefore, that in the solvolysis of 1-(2,6-dicarbomethoxyphenyl)ethyl bromide the carbomethoxy groups not only participate but they also force the creation of a geometric situation which is favorable for their participation, with an over-all effect on reaction rate which is pronounced.

Certain other explanations for the high reactivity of V, other than that presented, have been considered. It is possible, for example, that the compound solvolyzes unusually readily because of the relief of steric strain, which accompanies the activation process. However, the 2,6-dichloro analog VII, which is subject to much the same kind of strain, is not abnormally reactive. Conceivably a path might be followed in which the $-COOCH_3$ groups rotate out of the ring plane to permit the bonds to trigonal carbon in the activated complex to approach the ring plane with a resultant reduction in intensity of the unfavorable electronic effects of the carbomethoxy groups (as exerted through the ring) on C–Br bond rupture. The barrier to the attainment of the coplanar arrangement of ring and trigonal carbon cannot, however, by any means be overcome by carbomethoxy group rotation and it is very doubtful that such movement would have a significantly favorable rate effect. In view of the well-demonstrated capacity of o-COOR groups to become involved in related polar processes at adjacent aromatic side chains,[1,18] by far the most reasonable explanation for the relatively fast solvolysis rate of V is that in which o-$COOCH_3$ groups are assigned the role of intramolecular participants.

Thermodynamic Constants. Values of E_a and $\Delta S^{\ddagger}$ for hydrolysis of the various substituted benzyl and phenylethyl bromides which have been investigated are reported in Table III. Because of the limits of accuracy which are placed on the constants which are reported, a detailed discussion of their significance is not in order. The entropy loss accompanying the activation of 1-(2,6-dicarbomethoxyphenyl)ethyl bromide is substantially smaller than that for the reaction of the phenylethyl bromides and does deserve brief mention. Presumably participation of the carbome-

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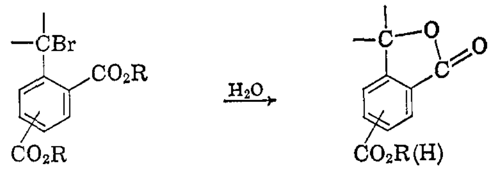
[17] In the structure shown for conformer a the electrons released by $-COOCH_3$ to the vacant p orbital at the reaction center are depicted as coming from a nonbonded orbital of carbonyl oxygen; D. J. Pasto and M. J. Lowe, *J. Am. Chem. Soc.*, 87, 1515 (1965), have presented evidence, based on a study of carbonyl participation in the silver ion assisted solvolyses of chloro ketones, of the involvement of nonbonded rather than π electrons of the $>C{=}O$ group. Previous work on the relative capacities of $-OR$ and $>C{=}O$ substituents to accelerate polar processes at adjacent aromatic side chains suggests that electrons are furnished by carbonyl rather than ether oxygen during $>COOCH_3$ participation; *cf.* L. J. Andrews, L. J. Spears, and R. M. Keefer, *ibid.*, **86**, 687 (1964).

[18] (a) L. J. Andrews and R. M. Keefer, *ibid.*, **81**, 4218 (1959); (b) R. M. Keefer and L. J. Andrews, *ibid.*, **81**, 5329 (1959).

thoxy groups in the reaction of V is extensive enough so that there is significantly less hydration of the activated complex and correspondingly less change in entropy than in the other reactions. The carbomethoxy groups themselves are probably very nearly properly positioned even before activation occurs. From the thermodynamic standpoint the unusual reactivity of V must be accounted for entirely in terms of the favorable entropy of activation, since the energy of activation for hydrolysis of this halide is as large as that for hydrolysis of any of the halides under consideration.

The Products of Hydrolysis of the Dicarbomethoxy-Substituted Benzyl and Phenylethyl Bromides. The product which has been isolated from the hydrolysis of *o*-carbomethoxybenzyl bromide is the lactone, phthalide.[1] It has not been established whether this is the immediate reaction product or whether *o*-carbomethoxybenzyl alcohol is first formed and is then converted to phthalide. Lactones have also been obtained by hydrolysis of the dicarbomethoxy-substituted benzyl and phenylethyl bromides (eq 2).



(2)

In some of the reactions, the second carbomethoxy group was hydrolyzed, undoubtedly through catalysis by hydrogen bromide generated in the solvolysis of the organic bromide.

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Some Relationships between the Hydrolysis of Imidate Esters and the Mechanisms of Related Acyl Transfer Reactions

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Abstract: Quantitative relationships are presented relating the effects of pH and general acid–base catalysts on the yields of the hydrolysis products of imidate esters to the rates and mechanisms of related acyl transfer reactions. Mechanisms including tetrahedral addition intermediates in acid–base equilibrium are found to account satisfactorily for parallel observations made in both types of systems. The kinetics of acyl transfer in O-acetylethanolamine are reinterpreted and conclusions are drawn concerning the influence of pH on the nature of the products formed by hydrolysis of 2-methylthiazoline, 2-methyloxazoline, and N-hydroxythioimidate esters.

The chemistry of the tetrahedral addition intermediates formed in many nucleophilic reactions at the acyl carbon atom has become the focus of intense investigation.[1] An understanding of the factors which control the formation and decomposition of these metastable intermediates should furnish the basis for a complete description of the acyl transfer reaction. For reactions in aqueous solution, particular attention must be directed at the following questions. (1) Do there exist several tetrahedral intermediates in acid–base equilibrium with each other? (2) What is the effect of pH variation on the distribution of these species? (3) What is the mode of decomposition of each species of the intermediate? (4) How is the decomposition of each species affected by the presence of general acid–base catalysts? Answers to the first three questions lead to a definition of the influence of pH on the nature of the rate-determining step. The understanding of the mechanism of general acid–base catalysis of the over-all reaction is dependent on the answer to the fourth question.

In earlier reports,[2–5] we have shown that studies of the hydrolysis of imidate esters provide valuable information concerning the mechanism of related acyl transfer reactions. If proton transfers are sufficiently rapid to allow acid–base equilibrium to occur between tetrahedral intermediates generated from different reactants (see, for example, Scheme I) knowledge of the behavior of the intermediates generated in imidate hydrolysis is sufficient for the complete kinetic description of the two related nucleophilic acyl transfer processes. The validity of this assumption has been partially demonstrated in one instance: the effects of

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[1] (a) M. L. Bender, *Chem. Rev.*, **60**, 53 (1960); (b) W. P. Jencks, *Progr. Phys. Org. Chem.*, **2**, 63 (1964); (c) T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," Vol. 1, W. A. Benjamin, Inc., New York, N. Y., 1966; (d) S. L. Johnson, *Advan. Phys. Org. Chem.*, **5**, 237 (1967).

[2] G. L. Schmir and B. A. Cunningham, *J. Am. Chem. Soc.*, **87**, 5692 (1965).

[3] B. A. Cunningham and G. L. Schmir, *ibid.*, **88**, 551 (1966).

[4] B. A. Cunningham and G. L. Schmir, *ibid.*, **89**, 917 (1967).

[5] R. K. Chaturvedi, A. E. MacMahon, and G. L. Schmir, *ibid.*, **89**, 6984 (1967).