TABLE I

Nuclear magnetic resonance data for antibiotic*

Shift (δ in p.p.m.)	Number of protons	Multiplicity	Assignment
1.05	3	Doublet (J = 7 Hz)	CH_3
1.80	2	Multiplet	Methylene at C-3
2.30	1	Broad multiplet	Methine at C-4
3.69	1	Doublet of doublets	Methine at C-2
5.10	2	Complex multiplet	Terminal methylene
5.83	1	Complex multiplet	Proton at C-5
4.72	3	Singlet	Protons exchanged with D_2O

*Determined in D_2O with a Varian A-60 instrument. Chemical shifts are relative to tetramethylsilane as internal standard.

+92; $[\theta]_{280}$, +138; $[\theta]_{260}$, +255; $[\theta]_{240}$, +590; $[\theta]_{220}$, +1840; $[\theta]_{216}$, +2130; $[\theta]_{214}$, +2130; $[\theta]_{212}$, +2080; $[\theta]_{210}$, +1815.

Anal. Calcd. for $C_7H_{13}NO_2$: C, 58.72; H, 9.15; N, 9.78. Found: C, 58.72; H, 9.43; N, 10.04.

Conversion of the Antibiotic to 3

The antibiotic (120 mg) was hydrogenated at room temperature and atmospheric pressure over 100 mg of palladium–charcoal (10%) catalyst in 95% ethanol. The theoretical quantity of hydrogen was absorbed within 30 min. The catalyst was removed by filtration and the residue obtained by evaporation of the filtrate *in vacuo* was treated with 30 ml of absolute ethanol saturated with dry HCl gas. The resulting solution was left for 2 h at room temperature then evaporated *in vacuo* to dryness. The residue was treated twice with ethanolic hydrochloric acid as above. Crystallization of the resulting solid from ethyl acetate afforded the ethyl ester hydrochloride **3** melting at 118–122 °C. The infrared (i.r.) spectrum (Nujol) had a series of bands between 3000 and 2500 cm^{-1} attributable to the ammonium ion. There was also a band at 1745 cm^{-1} due to the ester.

Anal. Calcd. for $C_9H_{20}ClNO_2$: C, 51.54; H, 9.61; Cl, 16.90; N, 6.68. Found: C, 51.26; H, 9.53; Cl, 16.89; N, 6.97.

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Carbon-13 kinetic isotope effects. V.[1] Substituent effects on k_{12}/k_{13} for alcoholysis of 1-phenyl-1-bromoethane

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As a test of our earlier interpretations of the ^{13}C kinetic isotope effects found for alcoholysis of 1-phenyl-1-bromoethane, we have examined the effect of the *p*-methyl and *p*-bromo substituents on the ^{13}C fractionations in ethanol and methanol. Isotopic fractionation at the α-carbon is found to be substituent dependent, and the observed trend is consistent with the proposal that stabilization of the cationic center by the phenyl ring is a major factor governing the isotope effect in these systems. The first example of an inverse primary kinetic isotope effect for carbon ($k_{12}/k_{13} < 1$) is described.

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Earlier it was found that k_{12}/k_{13} is 1.0065 for the methanolysis of 1-phenyl-1-bromoethane (**1**) at 25 °C (1). This relatively small isotope effect was attributed to resonance stabilization of the carbonium ion intermediate by the phenyl group, as well as to hyperconjugative interaction with the α-methyl group. The latter point has recently received support from measurements of the

[1]For Part IV, see ref. 4.

β-deuterium isotope effects in solvolyses of **1**, the corresponding chloride, and several substituted derivatives (2). Indirect support for the proposal of an appreciable influence of the phenyl ring on k_{12}/k_{13} has been presented by Kresge, Lichtin, Rao, and Weston (3) from their study of the dissociation of trityl chloride in liquid SO_2. In addition, crude calculations show (4) that the loss of the C—Br stretching mode in the initial state can be offset, in the transition state, by a reasonable degree of Ar—C^+ bond strengthening by π-overlap via resonance. Intuitively, stabilization by the phenyl ring should be governed by the polarity of ring substituents, and the present study was undertaken to examine the effect of *p*-methyl and *p*-bromo groups on k_{12}/k_{13} for alcoholysis to test our original proposal (1).

The ^{13}C isotope effects for 1-(4′-methylphenyl)-1-bromoethane in methanol and ethanol at 0° and for 1-(4-bromophenyl)-1-bromoethane in methanol at 0 and 25 °C were determined. The results are listed in Table I together with some data obtained previously (5).

As noted previously (1), there is evidence that the major path for alcoholysis of 1-phenyl-1-bromoethane itself is through an intimate ion-pair, i.e. the process is a limiting S_N1 reaction proceeding via a carbonium ion intermediate. A plot of the present kinetic data (see Experimental) for methanolysis at 0° *vs.* the σ^+ parameter yields a ρ value of −5.4 which is consistent with the foregoing. Thus, it is to be expected that generation of positive charge at the benzylic carbon will be assisted by resonance interaction with the phenyl ring, the extent of which may be governed by *p*-substituents. The methyl group should increase the interaction while a *p*-bromo atom should reduce electron supply from the aryl ring, both relative to **1**. If the fractionation at the benzylic carbon is sensitive to conjugative interaction with the aryl ring, as we have proposed (1), the k_{12}/k_{13} values should reflect this.

Of the reaction conditions examined, one is common to the three reactants, methanolysis at 0°, and it is clear that the isotope effect is largest for the electron-withdrawing *p*-Br group and smallest for the electron-releasing methyl substituent. In fact the latter value represents an inverse effect, i.e. the ^{13}C isotope reacts faster, and we believe this to be the first example of a primary inverse *kinetic* effect for carbon isotopy, although inverse equilibrium isotope effects for carbon have been reported (3). The precision of the present measurements is sufficient to establish that the trend from *p*-Me → *p*-Br is real. Further evidence is given by the 25° results for **1** and its *p*-bromo derivative.

As noted above, semi-quantitative estimations of the ^{13}C isotope effect for **1** in solvolysis have shown that the α-phenylethyl carbonium ion model for the transition state can accommodate the observed results, on the basis of the Bigeleisen formulation (6), and that a strengthening of the Ar—C^+ bond in the transition state can offset the loss of the C—Br stretching mode in the initial state (5). Arguments to support the view that the carbonium ion is an appropriate model have been presented (1). Kresge *et al.* (3) have shown, for the closely related dissociation of trityl chloride in sulfur dioxide, that the carbon–phenyl bonds in the triphenyl-carbonium ions must be much stronger than those in trityl chloride. These authors have discussed an extension of their reasoning to provide an explanation for the relatively small kinetic isotope effects found for S_N1 processes. As discussed in an earlier part of this series (5), it is difficult to make quantitative estimates of the magnitudes of the vibrational frequency differences for the

TABLE I

^{13}C kinetic isotope effects* in the alcoholyses of 1-(*p*-substituted phenyl)-1-bromoethane

	MeOH†		EtOH†	
	0°	25°	0°	25°
p-Me	−0.05 ± 0.05 (7)	—	0.05 ± 0.12 (6)	—
p-H	0.50 ± 0.04 (9)	0.65‡	0.18‡	0.44‡
p-Br	1.27 ± 0.06 (7)	1.13 ± 0.09 (12)	—	—

*$(k_{12}/k_{13} - 1)100$.
†Standard deviation of the mean is given with the number of separate runs in brackets.
‡From refs. 1 and 5.

change, initial state → transition state. It is gratifying, however, to find that the experimental results agree qualitatively with the predictions based on the model which is intuitively reasonable.

Although the correspondence between the experimental results for the substituent effect and the predicted trend appears to be intuitively satisfactory, there is another explanation of the fact that the carbon isotope effect is larger for the *p*-bromo derivative. If the reaction of 1-(4′-bromophenyl)-1-bromoethane with methanol does not proceed exclusively through a limiting carbonium ion mechanism, but rather involves the incursion of some nucleophilic character, the isotopic fractionation at the α-carbon would be expected to be greater than that found for a pure S_N1 process, on the basis of the available isotope effect data for processes believed to be "pure" S_N2 reactions (4, 7). For example, the S_N2 reaction of 1-phenyl-1-bromoethane with a ethoxide ion exhibits a carbon isotope effect of 3.2–3.6% over the temperature range 0–25 °C (4). Clearly, the 1.1–1.3% effect found for the *p*-bromo derivative over the same range is much smaller and somewhat less sensitive to a change in temperature. For the bimolecular displacements, k_{12}/k_{13} decreases with increasing temperature while the opposite trend is found for alcoholyses of 1-phenyl-1-bromoethane itself (5). Because the reactivity of the *p*-methyl derivative in alcohol limits the conveniently accessible temperatures at which determinations may be done, its isotope effect was measured only at a single temperature, 0 °C, in both ethanol and methanol. Of the three compounds, however, the *p*-methyl derivative is the most likely to exhibit truly limiting behavior.

In any event, on the available evidence it is not possible to decide whether the influence of these substituents on the carbon isotope effect is signalling a mechanistic shift from the limiting case for the *p*-methyl derivative to one in which there is some nucleophilic character for the *p*-bromo compound, or whether the substituents govern the degree of resonance stabilization in the carbonium ion. It can be noted that the α- and β-deuterium secondary isotope effects for a series of substituted α-phenylethyl chlorides and bromides undergoing solvolysis in aqueous solution, suggest that the reaction is partly nucleophilic for those reactants having electron-withdrawing substituents (2). It is reasonable to assume that the secondary deuterium effects for alcoholysis would exhibit similar behavior and it would be interesting to measure these effects.

Experimental

The methods employed in this study were somewhat modified from those described previously (1, 4, and 5). After quenching a given isotope effect run, the remaining bromide was hydrolyzed completely to α-phenylethyl alcohol by heating, with vigorous stirring, at 50–60° for 12 h with aqueous sodium carbonate before isolation of the ether by fractional distillation.[2] Gas–liquid chromatography and refractive index determinations were used to assess the purity of the isolated product. To compare the results obtained by this modification with our previous data, the isotope effect for methanolysis of 1-bromo-1-phenyl-ethane was redetermined at 0 °C and found to agree precisely with our earlier data.

The oxidative degradations to the benzoic acids were also modified in this work. For the *p*-methyl derivatives, oxidation to *p*-toluic acid was accomplished in the following way. The methyl ether (1 g) was added to an ice-cold solution of potassium dichromate (9 g) in 300 ml of 45% (w/w) sulfuric acid. The mixture was shaken for 30 min while warming to room temperature. After extraction with low-boiling petroleum ether (3 times), the combined extracts were washed with saturated sodium bicarbonate solution and dried. To the residue, after removal of the solvent in vacuum, was added a solution containing sodium hydroxide (5 g), sodium hypochlorite solution (100 ml of Javex), and water (200 ml). The mixture was shaken for 1 h at room temperature before the addition of sodium metabisulfite (15 g). After the addition of ice, concentrated hydrochloric acid (40 ml) was added and the *p*-toluic acid extracted with ether. Removal of the solvent afforded *p*-toluic acid in 92% yield, m.p. 177–179°, completely free of terephthalic acid.

The *p*-bromo derivatives were oxidized in a manner similar to that described previously (1) except that the manganese dioxide was not removed by filtration after completion of the oxidation. Instead the MnO_2 was destroyed, after the addition of 30% sulfuric acid, by the addition of sodium metabisulfite. The *p*-bromobenzoic acid precipitated from solution and was isolated by filtration in 95% yield, m.p. 253–254°.

As in the earlier work (1, 4, and 5), the kinetics were measured by acid–base titration, at least in duplicate, and the data are:

1-(4′-bromophenyl)-1-bromoethane. Methanolysis; $k_1 = 4.17 \times 10^{-7}$ s^{-1} (0°), 1.27×10^{-5} s^{-1} (25°).

1-(*p*-tolyl)-1-bromoethane. Ethanolysis; $k_1 = 7.81 \times 10^{-6}$ s^{-1} (0°); methanolysis, $k_1 = 1.07 \times 10^{-4}$ s^{-1} (0°).

[2]Within the limits of the methods employed, there is no evidence of styrene formation under these reaction conditions. Thus we conclude that the amount formed is much less than 1%.

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