1-Bromo-1-cyclopropylethane (5b). A solution of 28.0 g (106.8 mmol) of triphenylphosphine and 8.6 g (99.8 mmol) of **1b** in 0.12 L of DMF was treated with 16.0 g (100.1 mmol) of bromine and afforded 9.8 g (65.8 mmol, 66%) of **5b**.[3,5]

The initial distillate contained 3% alkenes which we assume was 5-bromo-2-pentene (**3b**) by comparison with an authentic sample.[18]

1-Bromo-1-cyclopropylpropane (5c). A solution of 11.4 g (43.5 mmol) of triphenylphosphine and 4.0 g (39.9 mmol) of **1c** in 50 mL of DMF was treated with 6.6 g (41.3 mmol) of bromine and afforded 5.0 g (30.7 mmol, 77%) of **5c**. Anal. Calcd for $C_6H_{11}Br$: C, 44.20; H, 6.80; Br, 49.01. Found: C, 44.38; H, 6.68; Br, 48.72.

The initial distillate contained 6% of alkenes which we assume was 1-bromo-3-hexene (**3c**) by comparison with an authentic sample.[18]

1-Bromo-1-cyclopropylbutane (5d). A solution of 12.5 g (47.7 mmol) of triphenylphosphine and 5.0 g (43.8 mmol) of **1d** in 60 mL of DMF was treated with 7.2 g (45.1 mmol) of bromine and afforded 6.0 g (33.9 mmol 77%) of **5d**. Anal. Calcd for $C_7H_{13}Br$: C, 47.48; H, 7.40; Br, 45.12. Found: C, 47.80; H, 7.61; Br, 45.39.

The initial distillate contained 7% of alkenes which we assume was 1-bromo-3-heptene (**3d**) by comparison with an authentic sample.[18]

1-Bromo-1-cyclopropylpentane (5e). A solution of 8.7 g (33.2 mmol) of triphenylphosphine and 4.0 g (31.2 mmol) of **1e** in 40 mL of DMF was treated with 5.0 g (31.3 mmol) of bromine and afforded 4.3 g (22.5 mmol, 72%) of **5e**. Anal. Calcd for $H_8H_{15}Br$: C, 50.28; H, 7.91; Br, 41.81. Found: C, 50.39; H, 7.94; Br, 41.52.

The initial distillate contained 5% of alkenes which we assume was 1-bromo-3-octene (**3e**) by comparison with an authentic sample.[18]

1-Bromo-1-cyclopropyl-2-methylpropane (5f). A solution of 25.0 g (95.3 mmol) of triphenylphosphine and 10.1 g (88.4 mmol) of **1f** in 0.115 L of DMF was treated with 14.3 g (89.5 mmol) of bromine and afforded 12.3 g (69.5 mmol, 79%) of **5f**. Anal. Calcd for $C_7H_{13}Br$: C, 47.48; H, 7.40; Br, 45.12. Found: C, 47.32; H, 7.24; Br, 45.34.

The initial distillate contained 7% of alkenes which we assume was 1-bromo-5-methyl-3-hexene (**3f**) by comparison with an authentic sample.[18]

1-Bromo-1-cyclopropyl-2,2-dimethylpropane (5g). A solution of 12.3 g (46.9 mmol) of triphenylphosphine and 5.5 g (42.9 mmol) of **1g** in 50 mL of DMF was treated with 7.1 g (44.4 mmol) of bromine and afforded 5.9 g (30.9 mmol, 72%) of **5g**. Anal. Calcd for $C_8H_{15}Br$: C, 50.28; H, 7.91; Br, 41.81; mol wt 190.0359. Found: C, 50.76; H, 8.05; Br, 40.74; mol wt 190.0351.

The initial distillate contained 2% of alkenes which we assume was 1-bromo-5,5-dimethyl-3-hexene (**3g**) by comparison with an authentic sample.[18]

Acknowledgment. We thank the Leo H. Baekeland Fund of the Research Corp. for funding of this work. We thank Gary Lavigne and Marvin Thompson, who performed the mass spectral analyses.

Registry No. **1a**, 2516-33-8; **1b**, 765-42-4; **1b** (ketone), 765-43-5; **1c**, 18729-46-9; **1c** (ketone), 6704-19-4; **1d**, 4426-61-3; **1d** (ketone), 6705-46-0; **1e**, 4379-16-2; **1e** (ketone), 14113-86-1; **1f**, 17393-35-0; **1f** (ketone), 6704-20-7; **1g**, 24382-76-1; **1g** (ketone), 20845-95-8; **4a**, 5911-08-0; **4b**, 10524-06-8; **4c**, 88106-23-4; **4d**, 88106-24-5; **4e**, 88106-25-6; **4f**, 88106-26-7; **4g**, 88106-27-8; **5a**, 7051-34-5; **5b**, 80204-20-2; **5c**, 88106-28-9; **5d**, 88106-29-0; **5e**, 88106-30-3; **5f**, 88106-31-4; **5g**, 88106-32-5; $Cl_3CCOCCl_3$, 116-16-5; Ph_3P, 603-35-0; Br_2, 7726-95-6; cyclopropyl cyanide, 5500-21-0; cyclopropanecarbonyl chloride, 4023-34-1.

Energetics of Carbonyl Addition and Elimination. Methoxide Ion with Esters[1]

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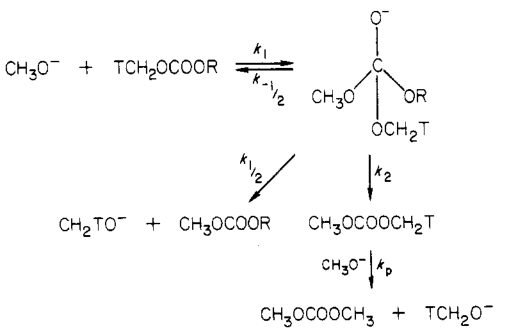
Tritium-labeled methyl benzoates, $CH_2TO_2CC_6H_4X$, lose the labeled methoxyl group in methoxide-containing methanol with $\Delta H^* = 11$–16 kcal mol^{-1}, $\Delta S^* = -17$ to -25 eu, $\rho_p = -2.4$, and retardation by ortho substituents. The similar exchange of dimethyl carbonate gives $\Delta H^* = 11$ kcal mol^{-1}, $\Delta S^* = -26$ eu. (−)-Menthyl methyl carbonate undergoes relatively rapid exchange and slow conversion to dimethyl carbonate ($k_{-1}/k_2 = 16$ at 45 °C and 18 at 36 °C), with $\Delta H^* = 16$ kcal mol^{-1}, $\Delta S^* = -17$ eu, for addition of methoxide ion, $\Delta H^* = 19$ kcal mol^{-1}, $\Delta S^* = -15$ eu, for overall formation of the transition state for elimination of menthoxide ion. It is concluded that the dominant transition states are for bond formation and fission and that these are characterized by ΔH^* around 10–20 kcal mol^{-1}, ΔS^* around −15 to −30 eu.

The reaction of strong nucleophiles with carbonyl substrates to produce displacement of a leaving group commonly occurs in a two-step manner, in which formation of the nucleophilic bond results in a tetrahedral intermediate (addition step), and the leaving group is then expelled with return of the carbonyl group to its trigonal form (elimination step).[2] Isotope exchange has been a useful technique in elucidating the relative importance of these two processes in limiting the rate. Especially straightforward in this regard is the exchange of a labeled methoxyl group of carbonate esters in basic methanol solution,[3] as in Scheme I. As opposed to ^{18}O exchange of carbonyl labeled esters in water, this system involves no ambiguities about the rapidity of proton switching among oxygens in the tetrahedral adduct. Thus it was possible to show that,

Scheme I



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[1] This research was supported by the National Institutes of Health and the National Science Foundation.

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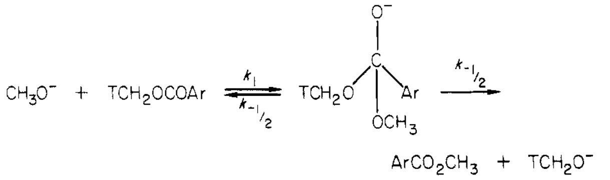
Table I. Second-Order Rate Constants for Methoxide-Catalyzed Loss of Radioactivity from $XC_6H_4CO_2CH_2T$ and $CH_3OCO_2CH_2T$ in Methanol at Various Temperatures

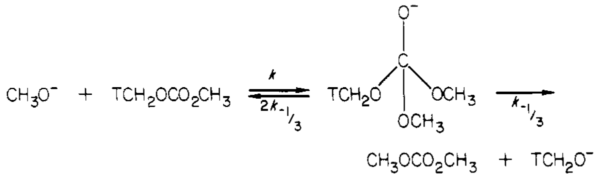
X	10^2k_X ± SD, M^{-1} s^{-1} (temp,[a] °C)		
p-CH_3O	0.38 ± 0.01 (25.1)	0.97 ± 0.01 (36.7)	1.80 ± 0.01 (45.1)
p-CH_3	0.97 ± 0.01 (27.4)	2.00 ± 0.01 (36.7)	3.74 ± 0.01 (45.2)
H[b]	1.75 ± 0.15 (25.0)	2.05 ± 0.04 (27.4)	4.56 ± 0.03 (37.0)
p-Br	1.82 ± 0.04 (6.8)	7.84 ± 0.23 (25.1)	17.9 ± 0.1 (36.7)
p-CO_2CH_3	18.1 ± 0.2 (25.2)	37.6 ± 0.8 (36.7)	
m-NO_2	110 ± 3 (27.4)		
p-NO_2	158 ± 5 (27.3)		
o-CH_3O	0.297 ± 0.005 (30.0)	0.545 ± 0.003 (36.7)	1.30 ± 0.01 (47.0)
o-CH_3	0.163 ± 0.001 (27.4)	0.347 ± 0.001 (36.7)	0.735 ± 0.001 (47.0)
o-Br	1.34 ± 0.02 (28.5)	2.25 ± 0.03 (36.7)	4.93 ± 0.04 (47.0)
(CH_3OCOCH_2T)	4.70 ± 0.14 (25.0)	8.00 ± 0.24 (36.0)	14.2 ± 0.4 (44.8)

[a] Temperatures precise to ±0.02 °C, accurate to ±0.05 °C. [b] $10^2k_2 = 8.95 \pm 0.05$ M^{-1} s^{-1} at 47.0 °C.

for R = p-$CH_3OC_6H_4$, C_6H_5, and p-$CHOC_6H_4$, 90–100% of the tetrahedral adduct undergoes elimination without reversion to reactants, so that addition is rate limiting.[3] Here we report results for methyl (−)-menthyl carbonate, where the competition for departure from the teterahedral adduct is between two alkoxy groups. We also present results for methoxyl exchange of methyl benzoates (eq 1) and dimethyl carbonate (eq 2). Taken together with other information, these data illuminate some features of the activation energetics of carbonyl displacement.



(1)



(2)

Results

Methoxyl Exchange of Methyl Benzoates and Dimethyl Carbonate in Methanol. This reaction was studied earlier by Jones and Sloane,[4] and our data are complementary. Tritium-labeled methyl benzoates were thermostated in methanolic lithium methoxide ([$LiOCH_3$] = 1–57 mM), and aliquots were taken at intervals and extracted with toluene, which was then washed. Radioactivity was lost in a first-order reaction, and the first-order rate constants were linear in [$LiOCH_3$] with small, usually negligible intercepts. The second-order rate constants k_x from such linear plots are given in Table I. The activation parameters are shown in Table II. Similar data are included for dimethyl carbonate.

Exchange and Methanolysis of Methyl (−)-Menthyl Carbonate. These reactions occur according to Scheme I with R = (−)-menthyl. The conversion of methyl (−)-menthyl carbonate to dimethyl carbonate can be followed polarimetrically,[5] while reversion of the tetrahedral intermediate can be followed by loss of radioactivity from the toluene-extractable ester. With methyl (−)-menthyl carbonate, exchange was found to occur considerably more slowly than exchange in the product dimethyl carbonate (for which the rate constant is given in Table I). The loss of extractable radioactivity therefore occurs as a first-order reaction at constant methoxide concentration. Variation of methoxide concentration then leads to a second-order rate constant $k_x = (4.62 \pm 0.14)10^{-3}$ M^{-1} s^{-1} (44.8 ± 0.1 °C) and $(2.20 \pm 0.07)10^{-3}$ M^{-1} s^{-1} (36.0 ± 0.01 °C). The methanolytic fission of the ester, studied polarimetrically, yields second-order rate constants $k_s = (5.18 \pm 0.16)10^{-4}$ M^{-1} s^{-1} (44.8 ± 0.1 °C) and $(2.24 \pm 0.07)10^{-4}$ μ^{-1} s^{-1} (36.0 ± 0.1 °C).

Table II. Activation Energetics[a] for Methoxide-Catalyzed Methoxyl-Exchange Reactions of $XC_6H_4CO_2CH_2T$ and $CH_3OCO_2CH_2T$ in Methanol

X	ΔH^*, kcal mol^{-1}	ΔS^*, cal K^{-1} mol^{-1}
p-CH_3O	13.9	−23
p-CH_3	13.8	−22
H	13.1	−23
p-Br	12.6	−21
p-CO_2CH_3	11.1	−25
o-CH_3O	16.1	−17
o-CH_3	14.1	−25
o-Br	12.9	−25
($CH_3OCO_2CH_2T$)	11.4	−26

[a] Standard states are 1 M for solutes and pure liquid for methanol. Enthalpies are reliable to better than 1 kcal mol^{-1} and entropies to better than 3 cal K^{-1} mol^{-1}.

From Scheme I, it is apparent that

$$k_x = k_1(k_{-1}/2 + k_2)/(k_{-1} + k_2) \qquad (3)$$

$$k_s = k_1k_2/(k_{-1} + k_2) \qquad (4)$$

$$k_x/k_s = 1 + (k_{-1}/2k_2) \qquad (5)$$

We then have from eq 5, $k_{-1}/k_2 = 15.8 \pm 0.8$ (44.8 °C) and 17.6 ± 0.9 (36.0 °C). For conversion of methoxide ion and ester to the addition transition state, we have

$$\Delta H^*_1 = 16 \pm 1 \text{ kcal mol}^{-1}$$

$$\Delta S^*_1 = -17 \pm 3 \text{ cal K}^{-1} \text{ mol}^{-1}$$

For conversion of methoxide ion and ester to the elimination transition state, we have

$$\Delta H_2^* = 19 \pm 1 \text{ kcal mol}^{-1}$$

$$\Delta S_2^* = -15 \pm 3 \text{ cal K}^{-1} \text{ mol}^{-1}$$

Discussion

Rate-Limiting Steps. In the course of displacement at carbonyl by a nucleophilic alkoxide ion, a series of transition states may be of kinetic significance, namely, those for (1) diffusion of reactants together, (2) solvent

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[4] The activation-parameter values for the p-OCH_3, p-CH_3H, and p-Br methyl benzoates agree roughly with those determined by Jones and Sloane: Jones, L. B.; Sloane, T. M. *Tetrahedron Lett.* **1966**, 831. Jones and Sloane obtained second-order rate constants by dividing first-order rate constants by methoxide concentration, a procedure that is shown to be valid by the small intercepts of our second-order plots.

[5] The polarimetric technique was used for studying the methanolysis of other menthyl esters by Taft et al.: Taft, R. W., Jr.; Newman, M. S.; Verhoek, F. H. *J. Am. Chem. Soc.* **1950**, *72*, 4511.

reorganization about reactants, (3) covalent-bond formation, (4) conformation reorganization in the tetrahedral intermediate, (5) covalent-bond fission, (6) solvent reorganization about products, and (7) diffusion of products apart.

Of the reaction studied here, two are identity reactions ($K_{eq} = 1.00$): methoxide exchange of methyl benzoates and of dimethyl carbonate. Such reactions must have identical transitions states for overall formation and dissociation of the tetrahedral intermediate, so that if diffusion solely limited the rate, the rate constants k_1 from eq 1 or 2 would be rate constants for diffusion. The data of Table I show that at 25 °C the second-order rate constants for exchange are $k_x = 1.75 \times 10^{-2}$ M^{-1} s^{-1} (methyl benzoate) and $k_x = 4.70 \times 10^{-2}$ M^{-1} s^{-1} (dimethyl carbonate). From eq 1, we have $k_1 = k_x/2 = 9 \times 10^{-3}$ M^{-1} s^{-1} (methyl benzoate) and from eq 2 $k_1 = k_x/3 = 1.6 \times 10^{-2}$ M^{-1} s^{-1} (dimethyl carbonate). These values are smaller than the expected diffusional rate constant[6] by factors of at least 10.[11] Thus the diffusional transition states for (1) and (7) are ruled out as primary determinants of the rate.

Solvent-reorganization transition states for (2) and (6) might in principle limit the rate. However, the data of Table I, extrapolated or interpolated where necessary to 25 °C, yield at this temperature a good correlation with simple Hammett σ constants, with $\rho = +2.4$ for para substituents. Such a large value (quite familiar for carbonyl displacements[7]) suggests substantial accumulation of negative charge in communication with remote substituents, which would not be consistent in any simple way with solvent reorganization alone limiting the rate. Ortho substituents also lead to somewhat slower reaction than the same substituent in the para position, whether electron releasing or electron attracting. This again is hard to reconcile with rate-limiting solvent reorganization.

Next we pass over (3) and (5), temporarily, to consider (4), conformational reorganization. One way of thinking about this possibility is to return to the substituent effect for the methyl benzoates and to consider the value of ρ in terms discussed by Hine.[8] Hine showed that ρ for a rate process can be thought of as a product of the change in σ value of the reacting functional group, as it is transformed from its reactant condition to its transition-state condition, with a transmission coefficient τ describing the efficiency of electronic interaction between reacting group and substituent (eq 6, where σ_R is the reactant-state value for the reacting group and σ_T its transition-state value).

$$\rho = \tau(\sigma_R - \sigma_T) \qquad (6)$$

Taking[9] $\sigma_R = 0.45$ and $\tau = 3.5$ for para substitution on a benzene ring,[8] we have $\sigma_T = -0.24$. This may be compared with[9] $\sigma_P = 0.0$, $\sigma_m = -0.1$ for $-CO_2^-$; $\sigma_m = 0.2$, $\sigma_p = 0.26$ for $-PO_3H^-$ $\sigma_p = +0.05$, $\sigma_m = +0.09$ for $-SO_3^-$. The transition-state reacting group is thus more electron releasing by a substantial amount than any of these negatively charged groups, *even* when they are *meta*, so that electron withdrawal by resonance is absent and the negative charge is closer. This suggests the reacting group in the transition state does not have the structure $-C(OCH_3)_2O^-$.

Finally, we argue that processes 3 and 5 are highly probably as major contributors to limitation of the rate. Here the covalent C–O bond to the nucleophile is incompletely formed, allowing delocalization of the negative charge into the ring, consistent with $\sigma_T = -0.24$. Partial formation of the tetrahedral adduct is consistent with steric retardation by ortho substituents. We will discuss elsewhere the evidence from solvent isotope effects and secondary hydrogen isotope effects, but we note here the heavy-atom isotope effects of O'Leary and Marlier[10] for the closely related reaction of hydroxide ion with methyl benzoate in water. The most important of these effects in the present context is the carbon isotope effect k_{12}/k_{13} of 1.043 ± 0.003 at the carbonyl-carbon center. This large effect is a near-certain signal of reaction–coordinate motion of this carbon and requires strong kinetic significance for transition states for bond formation and/or fission at the carbonyl group.

We conclude that a major contribution from transition states for bond formation or fission near the tetrahedral adduct must be present in these reactions. Smaller contributions from other types of transition state may also be present but cannot be dominant. The requirement for desolvation/resolvation of the strongly basic nucleophile and leaving group before and after, or in concert with, bonding alterations is not without *influence*, however. Energy changes associated with solvent reorganization distort the shapes of structure–reactivity relationships,[11-15] and the instability of the desolvated species may shift the structures of the transition states for bond formation or fission.[12,14]

Energetics of Addition and Elimination. In the methoxide-exchange reactions of methyl benzoates and dimethyl carbonate, the addition and elimination transition states are identical. The activation parameters of Table II suggest that a $\Delta H^* \sim -11$ to 16 kcal mol^{-1} and a $\Delta S^* \sim -17$ to -26 eu are characteristic of the conversion of ester and methoxide to such transition states in methanol.

For (–)-menthyl methyl carbonate, the combination of exchange and polarimetric rate data permitted the individual transition states to be characterized. Conversion of methoxide ion and ester to the addition transition state gave $\Delta H^* \sim 16$ kcal mol^{-1} and $\Delta S^* \sim -17$ eu; conversion to the less stable elimination transition state gave $\Delta H^* \sim 19$ kcal mol^{-1} and $\Delta S^* \sim -15$ eu. The addition transition state, with partial negative charge on the methoxide fragment, thus generates activation parameters in exactly the range seen for the similar methoxide-exchange transition states of benzoates and dimethyl carbonate. The elimination transition state, with parrtial negative charge on the menthoxide fragment, is less stable because of a higher enthalpy. Whether this arises because of the greater basicity of the secondary alkoxide, steric repulsions involving the bulky ring structure or steric inhibition of solvation we cannot say.

We conclude that formation in protic solvents of transition states for carbonyl addition and elimination, from alkyl esters and strongly basic nucleophiles, is characterized roughly by $\Delta H^* \sim 10$–20 kcal mol^{-1} and $\Delta S^* \sim -15$ to -30 eu. Similar values were observed by Taft et al. for various menthyl esters.[5] The range is also roughly the same for aryl esters.[3,16]

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Experimental Section

Labeled Esters. These compounds were prepared with either methanol-*t* (CH_2TOH) or water-*t* (HOT), both from New England Nuclear, as a source of tritium. Procedures were as follows: equilibration of unlabeled methyl esters with methanol-*t*; reaction of methanol-*t* with acyl chloride; and reaction of diazomethane with RCOOT, prepared by exchange with HOT. For example, dimethyl terephthalate (2.53, 0.013 mol) was added to 26 mL of CH_2TOH (1.8 μCi mmol^{-1}) and the solution was left for 12 h at room temperature. Water (50 mL) was added, and the crystals were removed by filtration: 2.2 g (88%) of $CH_3O_2CC_6H_4CO_2CH_2T$, mp 140–141 °C (lit.[17] mp 141.5–141.8 °C for the unlabeled compound), was obtained. Alternatively, anisoyl chloride (7.1 g, 0.04 mol) was added to methanol-*t* (4 mL, 0.1 mol; 1.8 μCi mmol^{-1}) and the mixture left for several days at room temperature. Then it was added to 100 mL of aqueous 5% Na_2CO_3; crystals were filtered out and recrystallized from 95% ethanol–water; yield of methyl anisate, 4.7 g (68%); mp 49–50 °C (lit.[18] mp 48 °C). Finally, benzoic acid (6.7 g, 0.05 mol) was allowed to stand for 3 h at room temperature in dioxane containing 1 mL of HOT (0.25 mCi/mL). The water and dioxane were pumped away, ether was added, and a solution of diazomethane in ether, prepared from nitrosomethylurea, was added. Methyl benzoate-*methyl-t* was distilled at 55–57 °C (0.5 mm); yield, 5.9 g (80%).

(−)-Menthyl methyl carbonate was prepared according to Salomaa[19] from (−)-menthol (15.6 g, 0.1 mol; Givaudan Delawanna, Inc.), which was converted to the alkoxide with sodium hydride in 200 mL of toluene. This was added dropwise to methyl chloroformate (13.6 g, 0.14 mol) in 100 mL of ether at 0 °C. Distillation and recrystallization from aqueous methanol yielded (−)-menthyl methylcarbonate, mp 32 °C (lit.[19] mp 31 °C).

Exchange Kinetics and Radioassay. Aliquots (1 mL) of reaction mixture were delivered by pipet into a separatory funnel containing 15 mL of xylene and 20 mL of water. After the mixture was shaken, the water was removed and the xylene layer extracted twice more with 20-mL portions of water and dried with sodium sulfate. A 10-mL aliquot of the xylene layer and a 10-mL aliquot of scintillation solution (10 g/L of 2.5-diphenyloxazole (PPO, Packard) in xylene or toluene) were combined in a Packard glass counting vial for radioassay. Packard-Tri-Carb or Beckman liquid scintillation counters were used. Observed radioactivities were fit to a first-order rate law by a weighted least-squares procedure. The first-order rate constants were then fit by a linear least-squares treatment to the methoxide concentrations to produce second-order rate constants.

Methanolysis of (−)-Menthyl Methyl Carbonate. Equal 1-mL volumes of substrate and sodium methoxide solutions were delivered by syringe into a thermostated 10-cm polarimeter cell (American Instrumental Co.), and the cell was quickly placed in a Perkin-Elmer digital polarimeter. Optical rotations (usually at 365 nm) were fit by a least-squares procedure to the first-order rate law. Second-order rate constants were obtained by linear least-squares as before.

Registry No. *p*-$MeOC_6H_4CO_2CH_2T$, 88229-69-0; *p*-$MeC_6H_4CO_2CH_2T$, 88229-70-3; $PhCO_2CH_2T$, 64935-86-0; *p*-$BrC_6H_4CO_2CH_2T$, 88229-71-4; *p*-$MeOCOC_6H_4CO_2CH_2T$, 88229-72-5; *m*-$O_2NC_6H_4CO_2CH_2T$, 88229-73-6; *p*-$O_2NC_6H_4CO_2CH_2T$, 88229-74-7; *o*-$MeOC_6H_4CO_2CH_2T$, 88229-75-8; *o*-$MeC_6H_4CO_2CH_2T$, 88229-76-9; *o*-$BrC_6H_4CO_2CH_2T$, 88229-77-0; $CH_3OCO_2CH_2T$, 88229-78-1; CH_2TOH, 20515-96-2; HOT, 13670-17-2; (−)-menthyl methyl carbonate, 22642-92-8; (−)-menthol, 2216-51-5; (−)-menthol sodium alkoxide, 27303-99-7; methyl chloroformate, 79-22-1; dimethyl terephthalate, 120-61-6; anisoyl chloride, 1300-64-7; benzoic acid, 65-85-0; diazomethane, 334-88-3.

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Antibacterial Benzisoxazolones. An Unusual Rearrangement Product from *o*-Nitrostyrene Oxide en Route to the Photolabile Carbonyl Protecting Group (*o*-Nitrophenyl)ethylene Glycol

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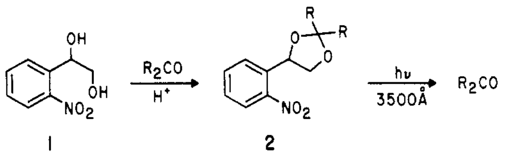
In the process of synthesizing the known, photolabile protecting group (*o*-nitrophenyl)ethylene glycol, we uncovered an acid-mediated rearrangement of *o*-nitrostyrene oxide to 1-(hydroxymethyl)-2,1-benzisoxazol-3(1*H*)-one. The structure was ascertained by IR, UV, ^1H NMR, ^{13}C NMR, MS, and X-ray crystallography. Also the benzisoxazolone was prepared by independent synthesis from an *o*-nitrobenzoate. Another novel transformation uncovered was the conversion of *o*-nitrostyrene oxide to 2-(*o*-nitrophenyl)ethanol with use of potassium hydroxide and 18-crown-6. Similar chemistry was insignificant with *p*-nitrostyrene oxide. The benzisoxazolone exhibited antibacterial and antileukemic activity (in vitro).

Introduction

As part of a program in our laboratories on the design and use of photolabile prodrugs for the therapy of psoriasis and other proliferative skin disorders, we were interested in the (*o*-nitrophenyl)ethylene glycol group (1) as a photoreactive protecting group for carbonyl moieties. The (*o*-nitrophenyl)ethylene acetal or ketal (2), formed from the glycol and a carbonyl group, readily regenerates the carbonyl group[2-4] with high quantum efficiency. In the process of preparing 1 we uncovered an interesting rearrangement to a benzisoxazolone that exhibited in vitro antibacterial and antileukemic activity.[5]



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