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Registry No.—1, 26452-84-6; 2, 14894-56-5.

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Aspects of Tautomerism. 6.[1a,b] Base-Catalyzed Hydrolysis of Pseudo Esters of γ-Keto Acids

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The rates of base-catalyzed hydrolysis of pseudo esters derived from γ-keto acids show strikingly poor sensitivity to the nature of the leaving group.[1a] The rates vary in the narrow range of about 12-fold as contrasted to a 10^3-fold spread of the corresponding benzoate esters. The results presented are consistent with a rate-determining formation of a tetrahedral intermediate (II) and its rapid collapse, by the cleavage of the lactone ring in a fast step.

The pseudo derivatives derived from γ- and δ-keto acids possess an interesting structural feature: the potential leaving group is not in conjugation with the carbonyl group. Therefore, the patterns of reactivity of pseudo esters may be expected to be quite different from that of normal carboxylic acid esters. In the base-catalyzed hydrolysis of carboxylic esters the leaving group has two functions, viz., (a) the conjugative function which stabilizes the ground state and decreases the carbonyl reactivity, (b) the ability to function as a leaving group. It turns out that a poor leaving group is also a good conjugative group leading to decreased reactivity of the carbonyl group on both counts.

Recently Bowden and Last[2] have reported the rates of alkaline hydrolysis of pseudo methyl esters of 8-acyl- and 8-aroyl-1-naphthoic acids and 5-formyl-1-phenanthroic acid. These authors favor a stepwise mechanism with the formation of the intermediate IV.

Newman and co-workers[3] have studied the effect of substitution in the aromatic rings with methyl groups on the rate of hydrolysis of pseudo methyl esters of *o*-benzoylbenzoic acids. Bender and co-workers[4] have studied the alkaline hydrolysis of 3-methoxyphthalide. In these studies, the effect of variation of leaving groups on the rates of hydrolysis has not been investigated. Although there is no reason to doubt that the mechanism involves the attack of hydroxide ion on the carbonyl group forming a tetrahedral intermediate, it is necessary to find out whether the reaction proceeds by a stepwise mechanism or by a concerted collapse of the lactone ring of the intermediate II (Scheme I, paths A and B).

In this paper we are reporting the results of alkaline hydrolysis of pseudo esters of *o*-benzoylbenzoic acid. The effect

Scheme I

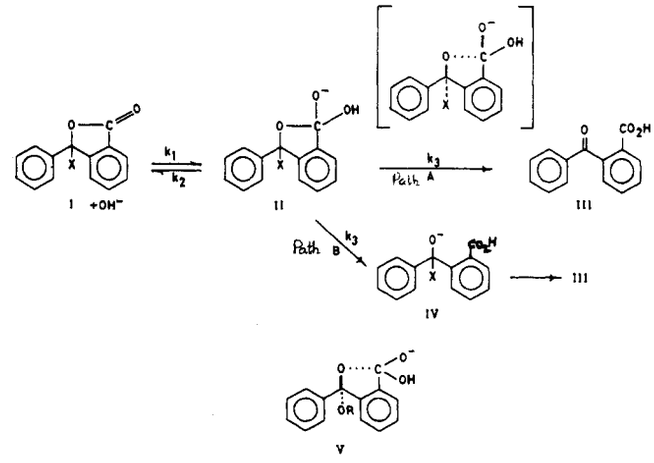

Table I. Rate Coefficients[a] for the Alkaline Hydrolysis of Pseudo Esters of o-Benzoylbenzoic Acid in 70% (v/v) Dioxane–Water

Registry no.	Leaving group (X)	$10k_2$, L mol^{-1} s^{-1} 25 °C	30 °C	35 °C	40 °C	Rel rate at 30.0 °C
7335-63-9	OMe	1.33	1.77	2.37		6.28
7498-89-7	OEt	0.979	1.18	1.58		4.2
5471-75-0	OPh	0.472	0.662	0.879	1.269	2.35
32524-74-6	Cyclopentyloxy	0.455	0.664	1.08		2.355
33632-03-0	Cyclohexyloxy		0.466	0.733	1.23	1.65
32524-75-7	*tert*-Butoxy	0.209	0.282	0.376		1.0
62930-12-5	Menthyloxy (*l,l*)		0.137	0.259	0.404	0.485
32524-79-1	Azido	2.31	3.36	5.01		1.2×10
62930-13-6	OC_6H_4Me-*p*		0.5	0.713	0.964	1.77
62930-14-7	OC_6H_4OMe-*p*		0.584			1.94
62930-15-8	OC_6H_4Cl-*p*		0.714	0.942	1.316	2.53
62930-16-9	$OC_6H_4NO_2$-*p*	0.692	1.17	2.067		4.14
	H[b]		0.951	1.55	2.27	

[a] Rate coefficients are reproducible within ±3%. [b] Rate coefficients for 3-phenylphthalide.

Table II. Rate Coefficients for the Hydrolysis of Benzoate Esters in 56% Acetone–Water (w/w) at 25 °C[6]

Registry no.	OR (leaving group)	10^3k_2, L mol^{-1} s^{-1}	Rel rate
93-58-3	OMe	9.022	6.8×10^2
93-89-0	OEt	2.891	2.1×10^2
774-65-2	*tert*-Butoxy	0.01327	1.0
32651-38-0	Cyclopentyloxy	0.3927	3.0×10
2412-73-9	Cyclohexyloxy	0.2679	2.0×10
93-99-2	OPh	37.67	2.8×10^3

of leaving group variation and the effect of substitution in the aromatic rings have been examined. Alkaline hydrolysis of some lactones of substituted *o*-benzoylbenzoic acids also has been studied for comparison.

Materials and Methods

The pseudo esters were prepared by treating the pseudo acid chloride of the γ-keto acid with the appropriate alcohol or phenol in the presence of a base like pyridine or sodium carbonate.[5] The lactones were prepared by reduction of the keto acid with sodium borohydride or with zinc and aqueous alkali. All kinetic experiments were carried out in 70% (v/v) dioxane–water.

Results and Discussion

Rate coefficients for the basic hydrolysis of a number of pseudo esters with various leaving groups are given in Table I alongside the relative rates. For purpose of comparison rates of hydrolysis of corresponding benzoate esters are presented in Table II.[6] The effect of substituents on the rate of hydrolysis of pseudo methyl esters and lactones of *o*-benzoylbenzoic acid is presented in Tables III and IV. Rates of hydrolysis of a few diastereomeric esters are presented separately in Table V. In Tables VI and VII are collected activation parameters for the hydrolysis of various pseudo esters and benzoate esters.

It is observed that pseudo esters are hydrolyzed faster than similarly constituted benzoate esters. For example, methyl pseudo *o*-benzoylbenzoate hydrolyzes 15 times faster than methyl benzoate and ethyl pseudo *o*-benzoylbenzoate hydrolyzes 34 times faster than ethyl benzoate at 25 °C (Tables I–III). This higher reactivity of pseudo esters is analogous to that of lactones. It could be attributed to their characteristic "cisoid arrangement" of the carbonyl dipole and the oxygen lone pair.[7,8,9a,b] It is found that the pseudo esters are generally hydrolyzed faster than the corresponding lactones (Table III).

Table III. Rate Coefficients[a] for the Alkaline Hydrolysis of A-Ring Substituted Pseudo Methyl Esters and Lactones of *o*-Benzoylbenzoic Acids[b]

Substituent	$10k_2$, L mol^{-1} s^{-1}, for pseudo methyl ester	Registry no.	$10k_2$, L mol^{-1} s^{-1}, for lactone	Registry no.
H	1.77		0.951	5398-11-8
4′-Cl	2.1	33433-81-7	1.31	4889-69-4
4′-Br	2.21	62930-17-0	1.69	25933-36-2
4′-Me			0.87	21615-75-8
4′-OMe			0.778	21615-74-7
4′-NMe_2	0.669	62930-18-1		
4′-NO_2	5.31	20656-57-9	3.33	20643-65-6

[a] See footnote for Table I. [b] Solvent, 70% (v/v) dioxane–water; temperature, 30.0 °C.

Table IV. Rate Coefficients[a] for the Alkaline Hydrolysis of B-Ring Substituted Pseudo Methyl Esters of *o*-Benzoylbenzoic Acids in 70% (v/v) Dioxane–Water at 30.0 °C

Registry no.	Substituent	$10k_2$, L mol^{-1} s^{-1}
62930-19-2	6-NO_2	68.92
40893-34-3	5-NO_2	101.50
62930-20-5	4-NO_2	114.60
	H	1.77
62930-21-6	6-NH_2	0.0405
62930-22-7	5-NH_2	0.615
62930-23-8	4-NH_2	0.0348

[a] See footnote for Table I.

The slightly faster rate is obviously due to the contribution of larger k_3 to the overall rate in pseudo esters compared to that of the lactone.

It can be seen from Table VI that the entropy of activation remains marginally affected or becomes more positive with increase in the bulk of the leaving group. This type of behavior is not observed for the alkaline hydrolysis of benzoate esters (Table VII). (For only two- to threefold difference in the rates of hydrolysis of some psuedo esters the enthalpy of activation changes by about 10 kcal mol^{-1} and entropy of activation by about 30 cal mol^{-1} K^{-1}. For example, see the activation parameters of methyl and menthyl pseudo esters of *o*-benzoylbenzoic acid in Table VI.)

The rates of hydrolysis of para-substituted phenyl pseudo

Table V. Rate Coefficients[a] for the Alkaline Hydrolysis of Diastereomeric Pseudo Esters of γ-Keto Acids in 70% (v/v) Dioxane–Water at 30.0 °C

R	X	$[\alpha]^{25}_D$	10^2k_2, L mol^{-1} s^{-1}
Ph	(−)-Menthol	−178	1.37
H[b]	(−)-Menthol	−170	5.63
H[b]	(−)-Menthol	+120	11.05
Ph	(−)-Cholesterol	+80	1.37
Ph	(−)-Cholesterol	−182	1.21

[a] See footnote for Table I. [b] Followed spectrophotometrically by monitoring the change in optical density for carboxylate anion at 330 nm.

Table VI. Activation Parameters[a] for the Alkaline Hydrolysis of Pseudo Esters of *o*-Benzoylbenzoic Acid in 70% (v/v) Dioxane–Water at 30.0 °C

Leaving group (X)	$\Delta H^{\ddagger}$, kcal mol^{-1}	$\Delta S^{\ddagger}$, cal mol^{-1} K^{-1}
OMe	9.47	−28.68
OEt	8.15	−33.9
OPh	11.52	−23.97
Cyclopentyloxy	15.6	−10.68
Cyclohexyloxy	17.83	−6.43
tert-Butoxy	10.14	−30.22
Azido	13.57	−13.98
$OC_6H_4CH_3$-*p*	11.89	−23.3
OC_6H_4Cl-*p*	9.63	−30.4
$OC_6H_4NO_2$-*p*	19.40	3.1
Menthyloxy (*l*,*l*)	19.98	0.8
H[b]	15.95	−8.63

[a] Values of $\Delta H^{\ddagger}$ are reproducible to within ±500 cal mol^{-1} and $\Delta S^{\ddagger}$ to within ±2 cal mol^{-1} K^{-1}. [b] 3-Phenylphthalide.

Table VII. Activation Parameters for the Hydrolysis of Benzoic Acid Esters in 56% (w/w) Acetone–Water at 25.0 °C[a]

OR (leaving group)	$\Delta H^{\ddagger}$, kcal mol^{-1}	$\Delta S^{\ddagger}$, cal mol^{-1} K^{-1}
tert-Butoxy	16.63	−22.87
Cyclohexyloxy	14.94	−23.15
Cyclopentyloxy	15.05	−21.43
OPh	13.70	−16.92
OEt	13.96	−21.15
OMe	13.85	−19.59

[a] Cf. ref 6.

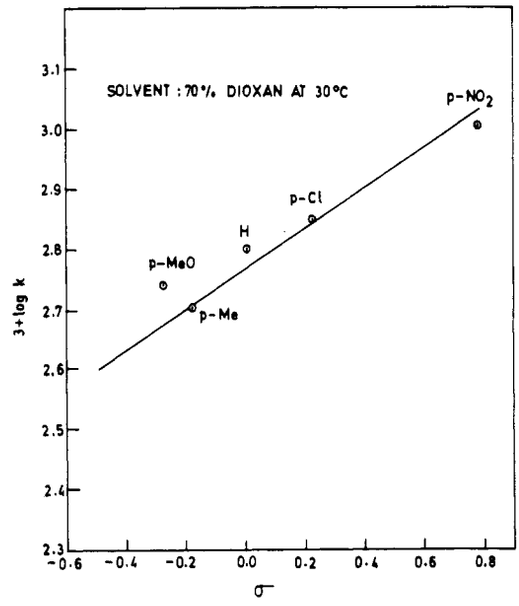

Figure 1. Hammett plot. Alkaline hydrolysis of substituted phenyl pseudo esters of *o*-benzoylbenzoic acid.

Table VIII. Activation Parameters for the Alkaline Hydrolysis of A-Ring Substituted Methyl Pseudo Esters of *o*-Benzoylbenzoic Acids in 70% (v/v) Dioxane–Water at 30.0 °C[a]

Substituent	$\Delta H^{\ddagger}$, kcal mol^{-1}	$\Delta S^{\ddagger}$, cal mol^{-1} K^{-1}
H	9.47	−28.65
4′-Cl	11.4	−22.1
4′-Br	12.3	−18.99
4′-NMe_2	17.7	−3.55
3′-NO_2	11.6	−19.52

[a] See footnote for Table VI.

Table IX. Activation Parameters for the Hydrolysis of Pseudo Methyl Esters of *o*-Formylbenzoic Acid[a]

Isomer with $[\alpha]^{25}_D$	$\Delta H^{\ddagger}$, kcal mol^{-1}	$\Delta S^{\ddagger}$, cal mol^{-1} K^{-1}
−170	12.31	−22.95
+120	11.80	−21.85

[a] See footnote for Table VI.

esters give a good correlation with the Hammett substituent parameter σ. The ρ value is 0.377 (γ = 0.986) (Figure 1). This, therefore, necessarily excludes correlation with the inductive parameter σ′ of Roberts and Moreland.[10] The small magnitude of the ρ value is consistent with the attack of hydroxide ion on the carbonyl group.

The rates of alkaline hydrolysis of pseudo esters of *o*-benzoylbenzoic acid with various leaving groups fall into such a narrow range that (maximum difference in rates is about 12-fold) no correlation exists between the rates and the substituent parameters like σ, σ*, and σ′.[11]

In view of the small influence of the leaving groups on the overall rate, we conclude that variation of k_1 (Scheme I) has a larger influence on rate than variation of k_3. Our results do not give much information on the nature of the events subsequent to the formation of the tetrahedral intermediate II (Scheme I).

We have observed that pseudo acid halides react with optically active alcohols to give unequal amounts of diastereoisomeric pseudo esters. The reaction of 3-bromophthalide with (−)-menthol gave a mixture of pseudo esters containing 60% of the diastereoisomeric pseudo ester with $[\alpha]^{25}_D$ +120° (mp 120–121 °C) and 40% of the isomer with $[\alpha]^{25}_D$ −170° (mp 116–118 °C). The differences in the rates of esterification arise clearly because of the difference in the steric environment in the transition state and may also be reflected in the relative stabilities of the two esters due to the disposition of the menthol moiety with respect to the chiral center of the pseudo acid residue. The diastereomer formed in larger amounts may be expected to have a sterically less crowded disposition.

We have studied the basic hydrolysis of a series of these esters (Table V). When the steric environment of dissymmetric alcohols at the nearby environment of the hydroxyl group is sufficiently dissimilar (with respect to the C–O axis or a plane passing through the C–O bond) as in menthol (and not cholesterol), it is observed that the ester more abundantly formed is the one that is hydrolyzed faster and the rate ratios for the formation of the esters and their reactions with base are more similar (about twofold for both reactions). One can conclude that the ground state steric hindrance causes the difference in the rates.

Effect of Substituents. A good linear correlation is ob-

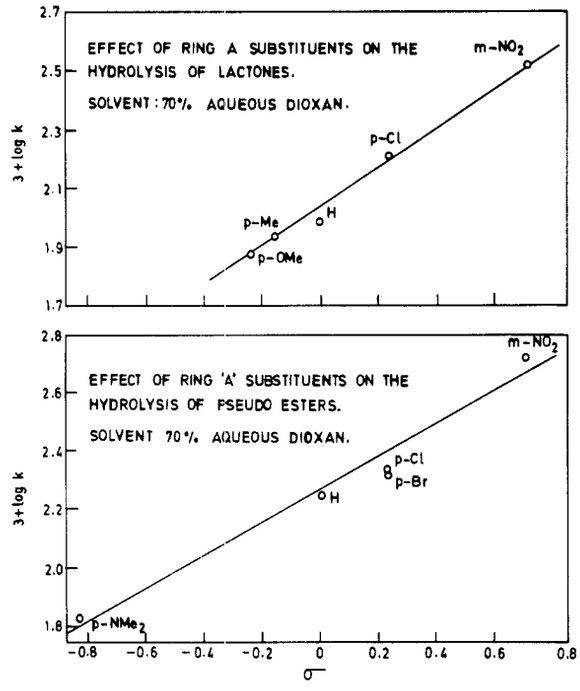

Figure 2. Hammett plot.

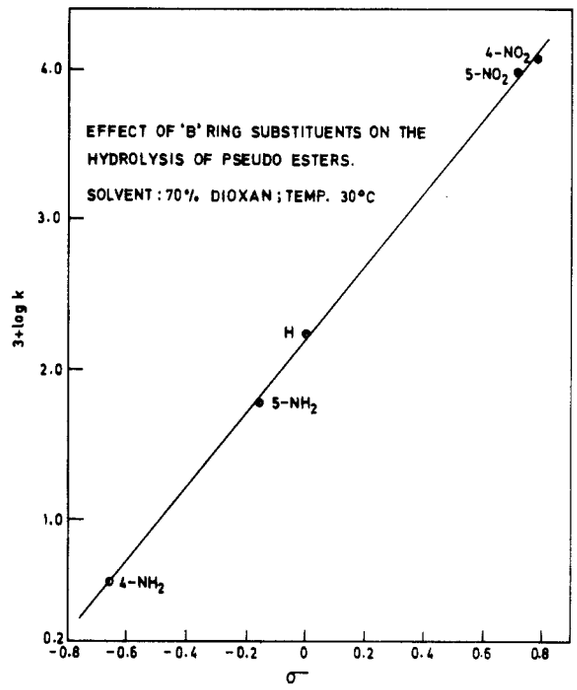

Figure 3. "Hammett plot".

tained when log k values for the hydrolysis of pseudo methyl esters and lactones of A-ring substituted o-benzoylbenzoic acids are plotted against Hammett σ values (Figure 2). The ρ values are 0.64 and 0.58 for pseudo esters and lactones, respectively (γ = 0.985 for pseudo esters and 0.985 for lactones). The small magnitude of ρ values indicates that the transmission of polar effects to the reaction center, namely, the carbonyl group, is not much.

The effect of B-ring substituents, on the other hand, is rather large. In this case also a good linear correlation exists between rates of hydrolysis and Hammett substituent parameters (Figure 3). The ρ value of 2.97 (γ = 0.997) is consistent with the attack localized on the carbonyl group rather than on the tetrahedral carbon atom. The ρ value in this case is somewhat higher than that for the hydrolysis of substituted benzoate esters (ρ = 2.2). This could arise from the fact that lactone carbonyl, being coplanar with the aromatic ring, is more susceptible to substituent influence. In the case of the 6-nitro and the 6-amino compounds steric effects of the substituents operate to modify the normal electronic effects. The steric effects manifest themselves in decreasing the steric hindrance to the carbonyl group from its neighbor and by decreasing the conjugation of the aromatic system with the carbonyl group and thereby increasing its reactivity.

In conclusion, our results demonstrate that the leaving groups in pseudo esters have an inconsequential influence on the overall rate. This is clearly due to their ejection in a fast step.

Experimental Section

All the melting points and boiling points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 700 instrument. NMR spectra were recorded with a T-60 Varian instrument. Hexane refers to the petrol fraction boiling at 40–60 °C.

All o-(p-substituted benzoyl)benzoic acids were prepared by following literature procedures.[9a,b] Preparations of the pseudo acid chloride of o-benzoylbenzoic acid and some of the esters have been reported earlier.[5,9a,b,12] The pseudo phenyl esters which are hitherto unreported were prepared by treating the acid chloride (0.2 mol in 40 mL of chloroform) with substituted phenols (0.2 mol in 40 mL of chloroform) in the presence of 2–3 mL of pyridine. The normal ester contaminants were separated either by crystallization or by column chromatography on silica gel. Table X summarizes the results.

Pseudo Methyl Esters of Substituted o-Benzoylbenzoic Acids. To a solution of the acid chloride in benzene (2.44 g in 30 mL) were added 100 mL of methanol and 2–3 mL of pyridine. After standing for 10 h the reaction mixture was worked up and the pseudo esters obtained were crystallized from benzene–hexane mixtures. The amino compounds were obtained by hydrogenation of the corresponding nitro esters in ethyl acetate in the presence of platinum oxide catalyst. The experimental results are presented in Table XI.

3-(p-Substituted phenyl)phthalides. Method A. The acid (20 mmol) was treated with 40 mmol of sodium borohydride in alcohol. After standing for a few hours the alcohol was distilled off and the residue was extracted with ether. The ethereal layer was washed with water and dried over anhydrous sodium sulfate. Evaporation of the solvent afforded the phthalide which was crystallized from benzene–hexane mixtures.

Method B. Reaction of 20 mmol of the acid with 5 g of zinc and 80 mL of 2 N potassium hydroxide solution gave the required phthalide (Table XII).

Pseudo Menthyl o-Benzoylbenzoate.[5c] o-Benzoylbenzoic acid chloride (4.8 g) in 40 mL of dry benzene was added to 3.2 g of menthol and 2 g of anhydrous sodium carbonate in 40 mL of benzene and refluxed on a steam bath for 6 h. After appropriate workup the yellow residue was crystallized from alcohol. The first crop gave pure pseudo (−)-menthyl (−)-o-benzoylbenzoate: mp 116–117 °C; $[\alpha]^{25}_{D}$ −187° (c 2.1, methanol); IR ν_{max} (Nujol) 1770 cm^{-1} (lactone carbonyl). Attempts to crystallize the other isomer were not successful.

Pseudo Cholesteryl o-Benzoylbenzoate. o-Benzoylbenzoic acid chloride (4.88 g) in 40 mL of benzene was treated with 6.4 g of cholesterol, 2 g of anhydrous sodium carbonate, and 40 mL of benzene and the mixture was refluxed on a steam bath for 6 h. The solid residue obtained after workup on crystallization from benzene–hexane yielded (−)-cholesteryl (−)-o-benzoylbenzoate (35%): mp 140–142 °C; $[\alpha]^{25}_{D}$ −180° (c 0.9, chloroform); IR ν_{max} (Nujol) 1775 cm^{-1} (lactone carbonyl).

Anal. Calcd for $C_{41}H_{54}O_3$: C, 83.78; H, 9.2. Found: C, 83.14; H, 9.39.

After rejecting some middle fractions the final crops of crystallization gave pseudo (−)-cholesteryl (+)-o-benzoylbenzoate (25%): mp 124–126 °C; $[\alpha]^{25}_{D}$ +80° (c 0.9, chloroform); IR ν_{max} (Nujol) 1775 cm^{-1} (lactone carbonyl).

Anal. Found: C, 82.37; H, 9.17.

Pseudo Menthyl o-Formylbenzoate. 3-Bromophthalide (8.25 g in 40 mL of benzene) was added to a mixture of (−)-menthol (6.1 g) and anhydrous sodium carbonate (4.8 g) in 40 mL of benzene and refluxed on a steam bath for 6 h. Fractional crystallization of the products in benzene–hexane gave at first pseudo (−)-menthyl (+)-o-formylbenzoate: mp 120–121 °C; $[\alpha]^{25}_{D}$ +120° (c 1.5, chloroform); IR ν_{max} (Nujol) 1770 cm^{-1} (lactone carbonyl); NMR ($CDCl_3$) 6.4 ppm

Table X. Pseudo Esters of *o*-Benzoylbenzoic Acid

Registry no.	Alcohol or phenol used	Yield, %	Mp, °C	IR ν_{max} (Nujol) (lactone carbonyl)	Molecular formula	Anal. Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
67-56-1	Methanol	90[a]	81–82[c]	1765	$C_{15}H_{12}O_3$						
64-17-5	Ethanol	95[b]	75–76[d]	1762	$C_{16}H_{14}O_3$						
108-93-0	Cyclohexanol	92	109–110[c]	1760	$C_{20}H_{20}O_3$	77.9	6.55		78.1	6.7	
96-41-3	Cyclopentanol	95	87–88	1767	$C_{19}H_{18}O_3$	77.5	6.15		77.45	6.3	
75-65-0	*tert*-Butyl alcohol	62[f]	95–96	1770	$C_{18}H_{18}O_3$	76.66	6.4		76.6	6.3	
108-95-2	Phenol[g]	95	158–160	1775	$C_{20}H_{14}O_3$	79.45	4.67		78.93	4.55	
100-02-7	*p*-Nitrophenol[h]	68	53–54	1770	$C_{20}H_{13}O_5N$	69.16	3.77	4.03	69.36	3.69	4.05
150-76-5	*p*-Methoxyphenol[h]	77	136–138	1790	$C_{21}H_{16}O_4$	75.89	4.85		75.98	5.2	
106-44-5	*p*-Cresol[h]	87	138–139	1790	$C_{21}H_{16}O_3$	79.93	5.1		79.82	5.33	
106-48-9	*p*-Chlorophenol	84	153–155	1785	$C_{20}H_{13}O_3Cl$						

[a,b] Solvent was alcohol itself. [c] Lit. mp 81–82 °C.[9b] [d] Lit. mp 83.0 °C [S. Wawzonek, H. A. Laitinen, and S. J. Kwiatkowski, *J. Am. Chem. Soc.*, **66**, 827 (1944)]. [e] Lit. mp 106–106.8 °C.[5c] [f] About 15% normal pseudo anhydride was formed in this reaction, mp 142 °C.[9b] [g] Lit. mp 162–163 °C (*footnote d*). [h] Separated from the normal ester contamination by column chromatography on silica gel.

Table XI. Pseudo Methyl Esters of Substituted *o*-Benzoylbenzoic Acids

Substituent	Mp, °C	Yield, %	IR ν_{max} (Nujol), cm^{-1} (lactone carbonyl)	Molecular formula	Anal. Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
6-NO_2	113–114	96	1760–1765	$C_{15}H_{11}O_5N$	63.16	3.89	4.9	63.16	3.86	5.08
5-NO_2	106–108	95	1780–1790	$C_{15}H_{11}O_5N$	63.16	3.89	4.9	63.08	3.79	4.94
4-NO_2	124–125	94	1800	$C_{15}H_{11}O_5N$	63.16	3.89	4.9	63.19	3.91	4.65
4′-NO_2	138–139	96	1760–1770	$C_{15}H_{11}O_5N$	63.16	3.89	4.9	63.45	3.78	5.1
6-NH_2	119–120	90	1740–1750	$C_{15}H_{13}O_3N$	70.58	5.1	5.32	70.5	5.13	5.49
5-NH_2	125–126	94	1770–1780	$C_{15}H_{13}O_3N$	70.58	5.1	5.32	70.74	5.0	5.18
4-NH_2	135–136	91	1760–1770	$C_{15}H_{13}O_3N$	70.58	5.1	5.32	70.6	5.17	5.42
4′-Br	93–94	91	1780–1785	$C_{15}H_{11}O_3Br$						
4′-Cl	101–102	96	1775–1780	$C_{15}H_{11}O_3Cl$						
4′-NMe_2	97–98	90	1760–1765	$C_{17}H_{17}O_3N$						

Table XII. 3-(*p*-Substituted phenyl)phthalides

Para substituent	Mp, °C	Yield, %	IR ν_{max} (Nujol), cm^{-1} (lactone carbonyl)
H[a]	115–116[c]	89	1775
4-Cl[a]	123–124	95	1740–1745
4′-OMe[b]	118–119	75	1750–1755
4′-Br[a]	138–139	70	1750–1755
4′-Me[b]	130–131	75	1775–1780

[a] Prepared by sodium borohydride reduction. [b] Prepared by reduction with zinc and alkali. [c] Lit. mp 113–114 and 115 °C [R. E. Risinger and J. A. Thomson, *Recl. Trav. Chim. Pays-Bas*, **82**, 801 (1963); F. Rotering and T. Zinke, *Ber.*, **9**, 631 (1876).

(phthalide proton s).

Anal. Calcd for $C_{18}H_{24}O_3$: C, 74.97; H, 8.39. Found: C, 74.52; H, 8.52.

After rejecting some middle fractions the final fractions of crystallization gave the other isomer: mp 116–118 °C; $[\alpha]^{25}D$ 170° (*c* 1.5, chloroform); IR ν_{max} (Nujol) 1770 cm^{-1} (lactone carbonyl); NMR ($CDCl_3$) 6.52 ppm (phthalide proton s).

Anal. Found: C, 74.6; H, 8.52.

(The compositions of the isomeric pseudo esters in the total mixture of the products were estimated from the relative intensities of the phthalide proton in the NMR spectrum with reference to the spectrum of one of the pure isomers.)

3-Phenyl-3-azidophthalide.[12] To a stirred suspension of sodium azide (1.3 g) in dimethylformamide (20 mL) was added a solution of *o*-benzoylbenzoyl chloride (2.44 g) in dimethylformamide (10 mL). Stirring was continued for 4 h. The mixture was diluted with ice-cold water and extracted with ether. Evaporation left 3-phenyl-3-azidophthalide (2.28 g): 90.8%; mp 56–57 °C (from hexane); IR ν_{max} (Nujol) 2140 (N_3) and 1780 (lactone carbonyl).

Kinetic Procedure. A titrimetric method was used to follow the hydrolysis of pseudo esters. Double distilled water was used to prepare all solutions. Dioxane was purified by the procedure of Fieser.[9c] The thermostat temperature was maintained to ±0.1 °C.

Standard solutions of the ester and the alkali were thermostated 1 h before the kinetic experiment. The alkali was added to the ester solution so that equal concentrations of the ester and hydroxide were obtained in 70% (v/v) dioxane–water. Half-delivery correction was applied when the alkali was added. The reaction was followed by withdrawing 5-mL aliquots at known intervals of time. The aliquots were run into a known volume of standard hydrochloric acid and the excess of HCl was titrated against alkali of known strength using a screened indicator consisting of a mixture of methylene blue and neutral red in alcohol. The rate constants were calculated from the slopes of plots of log $(a - x/b - x)$ vs. time.[13] In the case of phenyl pseudo esters the concentration of the ester was half that of alkali and the rate constants were calculated from the equation $dx/dt = k(a - x)(b - 2x)$ where a and b are concentrations of ester and alkali.

The kinetics of alkaline hydrolysis of pseudo esters of *o*-formyl benzoic acid was followed by measuring the change in the optical density with increasing concentration of carboxylate ion at 330 nm. The concentration of hydroxide ion was 20 times that of ester. The first-order rate constant was given by the slope of the plot log $(OD - OD_t)$ vs. time. The second-order rate is given by $k_2 = k_1/(OH^-)$.

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Registry No.—*o*-Benzoylbenzoic acid chloride, 22103-85-1; (−)-menthol, 89-79-2; cholesterol, 57-88-5; 3-bromophthalide, 6940-49-4; pseudo menthyl *o*-formylbenzoate isomer A, 62930-24-9; pseudo menthyl *o*-formylbenzoate isomer B, 62930-25-0; pseudo

cholesteryl o-benzoylbenzoate isomer A, 62930-26-1; pseudo cholesteryl o-benzoylbenzoate isomer B, 62961-06-2.

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Hydroboration. 47. Unique Stereospecificity of the Hydroboration of 1,3-Dimethylcycloalkenes with 9-Borabicyclo[3.3.1]nonane

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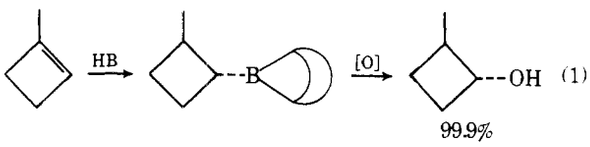
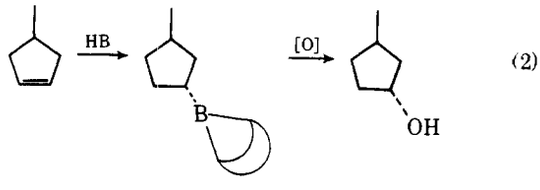
The hydroboration of 1,3-dimethylcycloalkenes **1–4** with 9-borabicyclo[3.3.1]nonane (9-BBN) proceeds with exceptionally high stereospecificity, affording only 2,ω-dimethylcycloalkyl-9-borabicyclo[3.3.1]nonane with both methyl groups trans to the 9-BBN moiety. For example, 1,3-dimethylcyclopentene is converted exclusively into *trans*-2,*trans*-5-dimethylcyclopentyl-9-borabicyclo[3.3.1]nonane. Stereochemical assignments are based on ^{13}C NMR spectra of the resulting organoboranes produced as well as on characterization of the alcohols derived from their oxidation. The synthetic utility of this remarkable stereospecific reaction is indicated by the ready conversion of the organoborane intermediates into the corresponding *cis*-2,ω-dimethylcycloalkanones and *trans*-2,*trans*-ω-dimethylcycloalkanols.

The hydroboration of cyclic olefins with 9-borabicyclo[3.3.1]nonane (9-BBN) proceeds with exceptionally high regio- and stereoselectivity.[2] Such hydroborations of 1-substituted cycloalkenes cleanly produce the *trans*-2-alkylcycloalkyl-9-borabicyclo[3.3.1]nonane. For example, hydroboration–oxidation of 1-methylcyclobutene yields 99.9% *trans*-2-methycyclobutanol (eq 1). Similarly, treatment of 3- or 4-



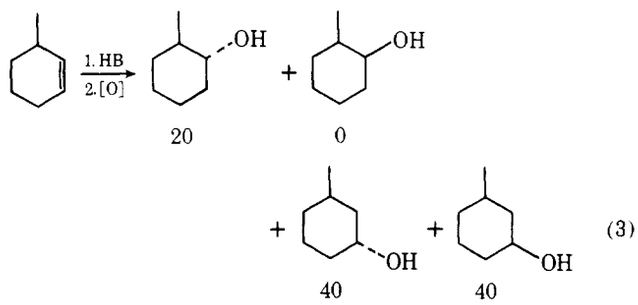
99.9% (1)

alkyl-substituted, 1,4-dialkyl-substituted cyclic olefins or of related exocyclic olefins with 9-BBN affords predominantly those products arising from addition to the least hindered side of the double bond. For example, 4-*tert*-butylcyclopentene is converted into *trans*-3-*tert*-butylcyclopentyl-9-borabicyclo[3.3.1]nonane, (99%), while 4-methylcyclopentene gives 3-methylcyclopentyl-9-borabicyclo[3.3.1]nonane (95%) (eq 2).



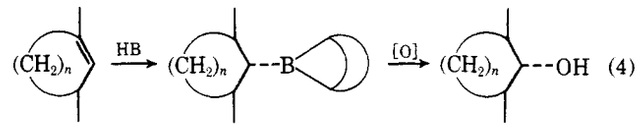
(2)

We recently reported the results of an extensive investigation into the regio- and stereochemistry of the hydroboration of representative cyclic olefins with 9-BBN.[2] During the course of this investigation, it was observed that hydroboration of 3-methylcyclopentene or 3-methylcyclohexene with 9-BBN produces no cis-1,2 isomer (eq 3). This unanticipated



(3)

result, coupled with the behavior of 1-methylcycloalkenes, led us to predict that 1,3-dimethylcycloalkenes should hydroborate to form exclusively the *trans*-2,*trans*-ω-dialkylcycloalkyl-9-borabicyclo[3.3.1]nonane derivatives (eq 4). Accordingly, we examined the stereochemistry of hydroboration of representative 1,3-dialkylcycloalkenes with 9-BBN.



(4)

The 1,3-dimethylcycloalkenes, **1–4**, were selected as representative for the examination of the validity of the high stereospecificity predicted for this reaction with 9-BBN.

Results and Discussion

General Procedure for Stereochemical Assignments. The hydroboration of olefins **1–4** was carried out to comple-