was cooled to 20 °C and extracted with ether (15 mL) to remove any unhydrolyzed material. The basic aqueous phase after acidification with iced HCl was extracted with ether (3 × 15 mL). The ether extract was washed with brine, dried ($MgSO_4$), and concentrated to afford the title compound as a white solid 85 mg (89%). Recrystallization from ether–pentane afforded a pure sample of this acid: mp 116–117 °C; ^1H NMR ($CDCl_3$) δ 1.5 (s, 3 H, CH_3), 3.46 (q, 2 H, J = 14 Hz, Ar H), 6.8–7.36 (m, 10 H, Ar H), 9.74 (br s, 1 H, COOH).

Reductive Alkylation of Methyl 2-Acetoxy-2-phenylacetate (19). Synthesis of Methyl 2-Ethyl-2-phenylacetate (20). To a stirred solution of the acetate **19** from methyl mandelate (144 mg, 0.69 mmol) in *anhydrous* THF (3 mL) was added a solution of sodium α(dimethylamino)naphthalenide in HMPA at 20 °C until a green color persisted for 30 s. The reaction mixture was then cooled (−10 °C), and EtI (0.129 g, 0.83 mmol) was added dropwise. The reaction mixture was then stirred for 2 h at −10 °C and then quenched with 10% HCl. The organic material was extracted with ether (3 × 20 mL). The ether extract was washed with 10% HCl (5 × 10 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated to afford a light brown oil (120 mg, 97%), which was identical with an authentic sample of **20** by GC comparison (15% FFAP on Chromosorb W 60/80, 4 ft × 0.25 in. column, at 160 °C) and by ^1H NMR.

Acknowledgment. We thank the National Science Foundation for financial support of this research.

Registry No. **1c**, 110-00-9; **1e**, 538-93-2; **1f**, 103-45-7; **1g**, 101-97-3; **1h**, 578-58-5; **1i**, 91-16-7; **1j**, 874-63-5; **1k**, 104-47-2; **1l**, 150-78-7; **1m**, 151-10-0; **1n**, 2398-37-0; **1o**, 95-46-5; **1p**, 1073-06-9; **1q**, 109-04-6; 1r, 90-11-9; **3b**, 83026-11-3; **3c**, 19377-69-6; **3d**, 83026-12-4; **3e**, 83026-13-5; **3f**, 83026-14-6; **3g**, 83026-15-7; **3h**, 83026-16-8; **3i**, 83026-17-9; **3j**, 83026-18-0; **3k**, 83026-19-1; **3l**, 83026-20-4; **3m**, 83026-21-5; **3n**, 83026-22-6; **3o**, 83026-23-7; **3p**, 83026-24-8; **3q**, 83026-25-9; **3r**, 83026-26-0; **4b**, 83026-27-1; **4c**, 83026-28-2; **4d**, 83026-29-3; **4e**, 83026-30-6; **4f**, 83026-31-7; **4h**, 83026-32-8; **4k**, 83026-33-9; **4l**, 83026-34-0; **4m**, 83026-35-1; **4n**, 83026-36-2; **4o**, 83026-37-3; **4q**, 83026-38-4; **5b**, 83026-39-5; **5c**, 40572-09-6; **5d**, 83026-40-8; **5e**, 23197-72-0; **5f**, 83026-41-9; **5h**, 4503-92-8; **5k**, 83026-42-0; **5l**, 33254-63-6; **5m**, 83026-43-1; **5n**, 50874-07-2; **5o**, 70484-46-7; **5q**, 39541-69-0; **6b**, 83026-44-2; **6d**, 83026-45-3; **6e**, 62707-18-0; **6h**, 83026-46-4; **6l**, 83026-47-5; **6n**, 83026-48-6; **6o**, 83026-49-7; 8, 56979-61-4; **9b**, 25899-90-5; **9d**, 18288-28-3; **9e**, 15687-27-1; **9h**, 83026-50-0; **9l**, 83026-51-1; **9n**, 3146-60-9; **9o**, 62835-95-4; **13**, 617-35-6; **14**, 78925-99-2; **15**, 78926-00-8; **16**, 78926-01-9; **17**, 4371-50-0; 18, 15206-55-0; **19**, 947-94-4; **20**, 2294-71-5; DEOM, 609-09-6; $SnCl_4$, 7646-78-8; methyl iodide, 74-88-4; *p*-bromotoluene, 106-38-7; methyl 2-hydroxy-2,3-diphenylpropionate, 83026-52-2; benzyl chloride, 100-44-7; methyl 2-acetoxy-2,3-diphenylpropionate, 41366-89-6; methyl 2,3-diphenylpropionate, 35030-49-0; methyl 2,3-diphenyl-2-methylpropionate, 57625-75-9; 2,3-diphenyl-2-methylpropionic acid, 7511-43-5; methyl mandelate, 771-90-4; ethyl iodide, 75-03-6.

Selective Reductions. 30. Effect of Cation and Solvent on the Reactivity of Saline Borohydrides for Reduction of Carboxylic Esters. Improved Procedures for the Conversion of Esters to Alcohols by Metal Borohydrides

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A comparative study of the relative reactivity of saline borohydrides (Li, Na, Ca) for the reduction of carboxylic esters has been made in selected solvents (ether, tetrahydrofuran, diglyme, 2-propanol, and ethanol) at 25 °C. In ether solvents the reactivity follows the trend $LiBH_4 > Ca(BH_4)_2 > NaBH_4$. On the other hand, in alcohol solvents the order of reactivity is $Ca(BH_4)_2 > LiBH_4 > NaBH_4$. The reactivities of $LiBH_4$ in ethyl ether and THF, of $Ca(BH_4)_2$ in THF and 2-propanol, and of $NaBH_4$ in ethanol proved to be promising for the reduction of esters. However, alcohol solvents are not useful for reductions at elevated temperatures because the decomposition of the reagents becomes competitive with the reduction. A convenient synthetic procedure has been developed for the rapid conversion of esters to alcohols by using $LiBH_4$ in ethyl ether, $LiBH_4$ in THF, and $Ca(BH_4)_2$ in THF and utilizing essentially stoichiometric amounts of the reagents. The procedure involves adding toluene to the reaction mixture and bringing the temperature to 100 °C while allowing the solvent do distill off. Following completion of the reaction, toluene is readily removed under vacuum and the reaction product hydrolyzed. These reductions were generally complete in 0.5–2.0 h, and high yields of alcohols (73–96%) were isolated. A number of ester derivatives, including compounds containing nitro, halo, cyano, and alkoxy groups, diesters, and lactones were reduced by this procedure. The study demonstrated the high selectivity of these reagents, permitting the rapid reduction of the ester group in the presence of many substituents. However, unsaturated esters undergo simultaneous hydroboration when reduced by this procedure.

Since its original discovery,[2] sodium borohydride has proven to be a very useful reagent for the selective reduction of aldehyde and ketone groups.[3] It has not been generally applicable for the reduction of ester and similar functional groups, which are relatively difficult to reduce. However, the reducing properties of sodium borohydride could be increased (1) by varying the solvent, (2) by changing the cation, (3) by the use of catalysts, and (4) by the presence of activating substituents.[4] Thus the successful reduction of esters by potassium borohydride and lithium chloride was first reported by Paul and Joseph.[5] Later, the reduction of esters by sodium borohydride was

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Table I. Solubility of Metal Borohydrides in Aprotic Solvents at 25 °C

metal borohydride	solubility[a] ether	THF	DG
$LiBH_4$	1.40	11.43	4.25
$NaBH_4$	0.0	0.02	1.67
$Ca(BH_4)_2$	0.09,[b] 0.4[b,c]	3.42	0.91

[a] The solubility is represented by the concentration of BH_4^- in molarity. [b] The concentration of BH_4^-. [c] $[BH_4^-]$ at reflux temperature.

Table II. Solubility of Metal Borohydrides in Protic Solvents at 25 °C

metal borohydride	solubility[a] ethanol	2-propanol
$LiBH_4$	>0.74[c]	1.46
$NaBH_4$	1.46[c]	0.08
$Ca(BH_4)_2$[b]	>1.0[c]	>1.0[c]

[a,b] See corresponding footnote in Table I. [c] Reacts with solvent.

achieved in the presence of metal salts such as LiI,[6] LiBr,[7] MgX_2 (X = Cl, Br),[7-9] $CaCl_2$[7], and $AlCl_3$.[9] The reducing agent in these cases could be the metal borohydride formed in situ according to 1 and 2.

$$NaBH_4 + LiBr \rightleftharpoons LiBH_4 + NaBr \quad (1)$$

$$2NaBH_4 + MX_2 \rightleftharpoons M(BH_4)_2 + 2NaX \quad (2)$$

$$M = Ca, Mg; X = Cl, Br$$

The reduction of esters by preformed lithium borohydride[10] and calcium borohydride[7] had also been demonstrated. Similarly, the enhanced reactivity of sodium borohydride in protic solvents[11] can be utilized for the reduction of esters. Presumably, the reaction involved loss of hydride, forming sodium alkoxyborohydrides, which are capable of reducing esters. Although several procedures have been developed for the reduction of esters, there has been no systematic study of the effect of solvent and cation on the reactivity of borohydride for such reductions. We have investigated in detail the reactivity of $LiBH_4$, $NaBH_4$, and $Ca(BH_4)_2$ in various solvents (ether, tetrahydrofuran, diglyme, 2-propanol, and ethanol) and have developed a convenient procedure for the selective conversion of esters to alcohols.

Results

Solubility and Stability of Metal Borohydrides in Aprotic (Ether) and Protic (Alcohol) Solvents. A saturated solution of the metal borohydride was prepared by stirring an excess of the reagent in the appropriate ethereal solvent at 25 °C overnight and then filtering the slurry. The concentration of borohydride in the clear solution was estimated by the hydrolysis method.[12] The results are given in Table I. The solutions appear to be stable indefinitely when protected from air and moisture. The solubility of $LiBH_4$ in ether solvents is quite high compared to that of $Ca(BH_4)_2$. However, $NaBH_4$ has significant solubility only in diglyme. Consequently, the solvents for $Ca(BH_4)_2$ are restricted to THF and diglyme, while the solvent for $NaBH_4$ is limited to diglyme.[12]

The protic solvents selected for this study are ethanol and 2-propanol. Methanol reacts rapidly with all of the metal borohydrides and hence is not useful as a reaction medium for a slow reduction. The solubility in 2-propanol was determined as described above. However, the solubility in ethanol was determined as follows. An excess of the reagent was stirred with the solvent at 0 °C overnight, and the mixture was warmed to 25 °C, filtered, and estimated. The results are given in Table II. $LiBH_4$ dissolves in 2-propanol, exhibiting no decomposition over 24 h. The solubility of $NaBH_4$ is very low in this solvent (0.08 M).[5] $Ca(BH_4)_2$ reacts slowly with 2-propanol (24% decomposition in 24 h). However, all of the metal borohydrides react with ethanol. The order of this decomposition is $Ca(BH_4)_2 \gg LiBH_4 > NaBH_4$. The results are given in Table III.

Rate of Reduction of Esters by Metal Borohydrides at 25 °C. Ethyl benzoate and ethyl caproate were selected as representative esters. In a typical reaction, 5.0 mmol of borohydride in the appropriate solvent was treated with 5.0 mmol of the ester at 25 °C. The total volume of the solution was adjusted to 5.0 mL. The resulting solution becomes 1.0 M in borohydride and 1.0 M in ester. In cases where clear solutions were realized, the course of the reaction was followed by determining the concentration of residual borohydride in aliquots of the reaction mixture at various time intervals. A blank reaction was performed under identical conditions, but without addition of compound. From the differences in the amounts of hydrogen evolved in these two experiments, the number of millimoles of hydride used for reduction per millimole of compound was calculated. In cases where the reaction mixture was a slurry, the rate was followed by conducting the experiment under identical conditions in individual flasks, hydrolyzing the entire reaction mixture to obtain the residual hydride concentration. The results are given in Table IV.

Effect of Solvent. The study indicates that the reduction of esters by $LiBH_4$ in the various sovlents, other than ethanol, follows a regular trend. The reactivity of $LiBH_4$ is greatest in media of low dielectric constant. Increasing the polarity decreases the reactivity. Thus, the order of reactivity is $LiBH_4$ in ether > THF ≈ DG > *i*-PrOH. Indeed, the reduction of esters by $LiBH_4$ in ethyl ether is considerably faster than in the other solvents.

$Ca(BH_4)_2$ also follows a regular trend in the reactivity. However, here the trend is opposite that of $LiBH_4$: $Ca(BH_4)_2$ in *i*-PrOH > DG > THF > Et_2O (partially soluble). It should be noted that $Ca(BH_4)_2$, unlike $LiBH_4$, reacts slowly with 2-propanol (24% in 24 h). Also, the solubility of $Ca(BH_4)_2$ in ether is very low, which could be responsible for the relatively low apparent reactivity in that medium.

$NaBH_4$ is more reactive in diglyme than in THF, ethyl ether, or 2-propanol, probably due to its solubility in the former solvents. Because of its low solubility in the other solvents, it is not possible to establish a trend, as for $LiBH_4$ and $Ca(BH_4)_2$ above.

The metal borohydrides are all soluble in ethanol (Table II). The rates of decomposition of metal borohydrides in ethanol follow the order $Ca(BH_4)_2 \gg LiBH_4 > NaBH_4$. The rates of reduction of esters also follow the same trend: $LiBH_4 > NaBH_4$. The reduction of esters by $Ca(BH_4)_2$ in

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Table III. Rate of Decomposition of Borohydride[a] by Alcohols

metal borohydride	% reaction[b] time for EtOH, h 0.5	1	2	4	8	24	time for 2-propanol, h 0.5	1	2	4	8	24
$LiBH_4$	5	11	*c*			100[d]		2	2			2
$NaBH_4$			2	8	20	53[e]						0.1
$NaBH_4$[f]	29[d]				100[d]							
$Ca(BH_4)_2$	85[d]	95[d]	100[d]						7		16	23
$Ca(BH_4)_2$[f]							43[d]	56[d]		96[d]		

[a] The amount of borohydride (BH_4^-) present is sufficient to give a 1.0 M solution if it dissolved; reaction was at 25 °C, unless otherwise indicated. [b] Percent of reaction is based on hydride estimation, unless otherwise indicated. [c] White precipitate formed. [d] Percent of reaction based on hydrogen evolution. [e] 19 h. [f] At reflux temperature.

Table IV. Rate of Reduction of Esters by Metal Borohydrides in Different Solvents at 25 °C[a]

ester	solvent	% reaction[b] time for $LiBH_4$, h 0.5	1	2	4	8	24	time for $NaBH_4$, h 0.5	1	2	4	8	24	time for $Ca(BH_4)_2$, h 0.5	1	2	4	8	24
ethyl caproate	ether	17	28	41	65	100		no reaction[c]						*c*					13
	THF	5	10	21	29	48	61			*c*			5		6		8	14	29
	DG		14	22		40	56		2	3	5	9	12		6	10	16	26	44
	i-PrOH		3	12	23	38	*d*	*c*		3	3	4	7	8	14	21	42	57	73
	EtOH	11	42	*d, e*				*e*		8	28	66	98[f]	*e*					
ethyl benzoate	ether	9	14	19	31	49	*d*	no reaction[c]						*c*					8
	THF		12		20	32	43	insignificant[c]							1		6	12	21
	DG		10		18	28	40		2	2	3	6	10		2	5	10	18	30
	i-PrOH			2	3	9	*d*						5	*e*	5	8	14	24	38
	EtOH	4	16	*d, e*				*e*		4	20	51	69	*e*					

[a] [Ester] = [BH_4^-] = 1.0 M (5 mmol). [b] Percent of reaction is based on hydride estimation, unless otherwise indicated. [c] Heterogeneous mixture. [d] White precipitate formed. [e] Reacts with solvent. [f] 20 h.

Table V. Rate of Reduction of Esters by Borohydride at Reflux Temperature of the Solvent[a]

ester	solvent	% reaction time for $LiBH_4$, h 0.5	1	2	4	8	time for $NaBH_4$, h 0.5	1	3	5	8	time for $Ca(BH_4)_2$, h 0.5	1	2	4	8
ethyl caproate	ether	26	41	61	90	99[b]										
	THF	37	53	76	100							21	28	42	61	82
	i-PrOH											33	41[c]			
	EtOH						16	35[c]								
ethyl benzoate	ether	12	20	30	44	67										
	THF	33	45	67	88	100						18	26	40	61	83

[a] [Ester] = [BH_4^-] = 1.0 M. [b] 5 h. [c] See Table III for the blank reaction.

ethanol could not be studied since hydride is lost quite rapidly at 25 °C (85% in 0.5 h). Kollonitsch did achieve reductions of reactive esters at lower temperatures (~−10 to −20 °C).[7] The data appear to indicate a parallelism in alcohol solvents between instability of the metal borohydride solutions and their effectiveness for the reduction of esters.

Effect of Cation. Since the borohydrides are not uniformly soluble in all of these solvents, a comparison is made only between homogeneous reactions under identical conditions. The results indicate that in ether solvents $LiBH_4$ exhibits greater reactivity for ester reduction than the other salts. Thus, in diglyme, the trend is $LiBH_4 > Ca(BH_4)_2 > NaBH_4$. Similarly, in THF the reactivity order is $LiBH_4 > Ca(BH_4)_2$. On the other hand in 2-propanol, $Ca(BH_4)_2$ is more reactive than $LiBH_4$. In ethanol the decomposition of $Ca(BH_4)_2$ is very rapid, suggesting that here also it may be more reactive than $LiBH_4$. In ethanol protonolysis of $LiBH_4$ is faster than that of $NaBH_4$. Similarly, in this solvent $LiBH_4$ reduces esters faster than $NaBH_4$.

Rate of Reduction of Esters by Metal Borohydride at Reflux Temperature. The results described above demonstrate the ability of metal borohydrides to reduce esters in various solvents. On the basis of their favorable reactivities, the following systems were chosen for further studies to develop a suitable procedure for the reduction of esters: (i) $LiBH_4$ in ether, (ii) $LiBH_4$ in THF, (iii) $Ca(BH_4)_2$ in THF, (iv) $Ca(BH_4)_2$ in 2-propanol, (v) $NaBH_4$ in ethanol. The rates of reduction of esters in these systems were studied at the reflux temperature of the solvent by following the same procedure described earlier. The results are given in Table V.

The data show that $LiBH_4$ is more reactive than $Ca(BH_4)_2$ in refluxing THF. Thus, while $LiBH_4$ reduced ethyl caproate completely in 4 h, only 60% reduction was observed in this time with $Ca(BH_4)_2$. Nevertheless, $Ca(BH_4)_2$ in THF is a useful system for the reduction of esters.

In alcohol solvents, the metal borohydrides undergo decomposition that is much more rapid than the reduction of even the more reactive esters studied. Thus, in a reaction between ethyl caproate and $Ca(BH_4)_2$ in refluxing 2-propanol, only 41% of the ester was reduced in 1 h. However, a blank reaction under identical conditions indicated 56% decomposition of borohydride in the same time. Similarly, in the case of $NaBH_4$ reduction of ethyl caproate in refluxing ethanol, a solid material formed in 1 h. Analysis by GLC after hydrolysis indicated only 35%

Table VI. Reduction of Esters by Metal Borohydrides by Following Procedures A-C[a]

ester	product	time, h			% yield[b]		
		A	B	C	A	B	C
ethyl caproate	1-hexanol	0.25	0.25	1.5	86 (100)	89 (100)	86 (99)
ethyl benzoate	benzyl alcohol	1.0	1.0	1.5	90 (100)	87 (98)	87 (98)
ethyl phenylacetate	2-phenylethanol	1.0	1.0	1.5	92	91	87
ethyl cyclohexanecarboxylate	cyclohexylcarbinol	1.0	1.5	1.0	91 (100)	85 (100)	89 (99)
ethyl adamantane-1-carboxylate	1-adamantylcarbinol	5.0	5.0	10.0	96 (99)	90 (99)	90 (96)
ethyl *p*-chlorobenzoate	*p*-chlorobenzyl alcohol	0.5	0.5	1.0	90	95	95
ethyl *m*-bromobenzoate	*m*-bromobenzyl alcohol	0.5	0.5	1.0	94	96	92
ethyl *p*-nitrobenzoate	*p*-nitrobenzyl alcohol	0.25	0.25	0.5	70	73	72
ethyl *m*-cyanobenzoate	*m*-cyanobenzyl alcohol	0.5	0.5	1.0	62	63	70
ethyl *p*-methoxybenzoate	*p*-methoxybenzyl alcohol	2.0	2.5	18.0	96	94	(88)
ethyl *m*-methoxybenzoate	*m*-methoxybenzyl alcohol	0.5	0.5	1.0	95	95	94
ethyl trichloroacetate	2,2,2-trichloroethanol	0.25[c]	0.25[c]	0.5[c]	80	79	78 (97)
diethyl dimethylmalonate	2,2-dimethyl-1,3-propanediol	0.25[c]	0.25[c]	0.5[c]	83	81	79
γ-butyrolactone	1,4-butanediol	0.25	0.25	0.5	86	84	84
phthalide	phthalyl alcohol	0.5	0.5	4.0	90	91	90

[a] Ester = 25 mmol; BH_4^- = 13.75 mmol; temperature 100 °C; solvent being distilled off. Procedures: A, $LiBH_4$ in ether and 4 mL toluene; B, $LiBH_4$ in THF and 4 mL toluene; C, $Ca(BH_4)_2$ in THF and 4 mL toluene. [b] Yield of pure isolated product. Values in parentheses represent GLC values. [c] At 25 °C; hence, no toluene was added for the isolation run.

alcohol. On the other hand, the blank reaction under identical conditions indicated 29% decomposition of the salt in 0.5 h.

It is evident from this study that protic solvents are not generally useful for the effective conversion of esters to alcohols by borohydride salts. On the other hand, ether solvents (ether, THF) proved to be promising for the reduction of esters by $LiBH_4$ and $Ca(BH_4)_2$. At higher temperatures, the reaction is quite rapid.[8] Hence, we undertook to develop a convenient procedure for the reduction of esters using metal borohydrides at 100 °C. Toluene is added to keep the reaction mixture in a fluid state, and the volatile solvent is distilled off to bring the temperature to 100 °C.

General Procedure for the Reduction of Esters Using $LiBH_4$ in Ethyl Ether. Procedure A. In a typical experiment, to the reaction flask containing 13.75 mmol of borohydride, 25 mmol of ester, and ~7.5 mL of ethyl ether was introduced 4 mL of toluene. (Toluene was added to avoid caking of the residue and to serve as a heat-transfer medium.) The flask was connected to a distillation setup under nitrogen and heated on an oil bath to 100 °C. The solvent (ethyl ether) was distilled off and collected in a measuring cylinder (7.5 mL). The reaction was monitored by hydrolyzing the entire residue, extracting the organic components into ether, and analyzing the dried ether layer by GLC. Similar runs were conducted at various time intervals to establish the time required for completion of the reaction. The absence of any peak corresponding to the ester indicates completion of the reaction. A large number of esters were studied in order to explore the selectivity of the procedure. Under these conditions, the reductions were fast, being complete usually in 0.25–1 h.

For isolation of the product, a separate experiment was performed. The reaction was allowed to proceed for an appropriate time sufficient to achieve complete reduction as established previously. Toluene was then distilled off at 100 °C under reduced pressure. (The removal of toluene before hydrolysis avoids possible contamination of the product by the hydrocarbon.) Hydrolysis of the borate complex then produces the alcohol in essentially quantitative yield. The results are given in Table VI.

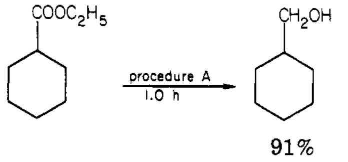
Reduction of Esters by $LiBH_4$ in THF. Procedure B. The procedure followed is essentially the same as above. The reduction described above was applied for isolation of the product. The results are also presented in Table VI.

Reduction of Esters by $Ca(BH_4)_2$ in THF. Procedure C. By use of the above procedure, the model esters were reduced in 0.5–1.5 h. The results are reported in Table VI.

Synthetic Applications. Aliphatic esters are reduced rapidly in this procedure. For example, ethyl caproate is reduced in 0.25 h (procedure A), producing an essentially quantitative yield of alcohol after hydrolysis (eq 3).

$$CH_3(CH_2)_4COOC_2H_5 \xrightarrow[0.25\ h]{A} \underset{86\%\ (100\%\ GLC)}{CH_3(CH_2)_4CH_2OH} \quad (3)$$

The procedure could be applied to the reduction of cyclic and sterically hindered esters. However, longer time intervals were necessary for complete reduction of hindered esters such as ethyl adamantanecarboxylate (Table VI), eq 4 and 5



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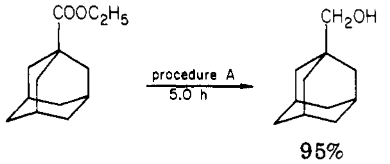
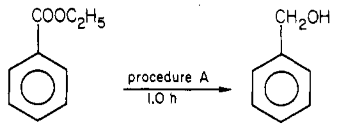
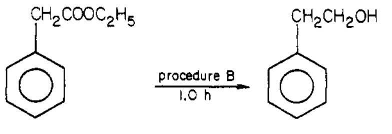


(5)

Aromatic esters are also readily reduced (eq 6 and 7).

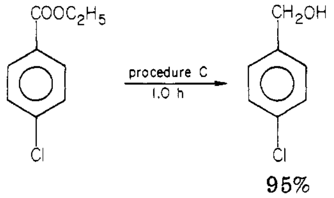


(6)

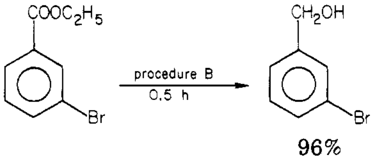


(7)

The reagents are highly selective and tolerate the presence of a number of potentially reducible groups, which gives this procedure some advantages over the use of lithium aluminum hydride (eq 8–12).



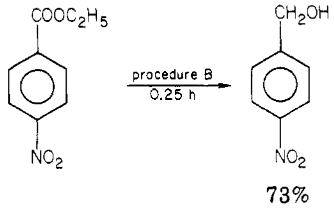
(8)



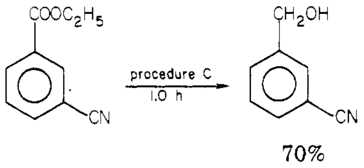
(9)

$$CCl_3COOC_2H_5 \xrightarrow[\text{0.25 h, 25 °C}]{\text{procedure A}} CCl_3CH_2OH \quad (10)$$

80%

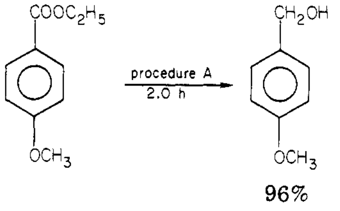


(11)



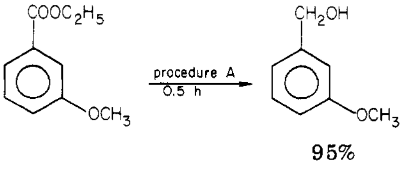
(12)

The foregoing study also indicates that structural modifications affect the rate to some extent. Thus, electron-withdrawing substituents such as nitro, chloro, bromo, cyano, etc. accelerate the reaction rate, while electron-releasing groups such as methoxy retard the rate. Thus, ethyl *p*-methoxybenzoate required 2.0 h for complete reduction. The alcohol was obtained in 96% yield (eq 13).



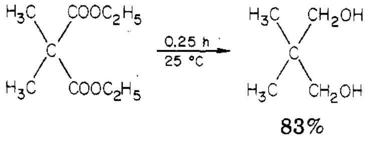
(13)

As expected, the *m*-methoxy derivative reacts faster (eq 14).



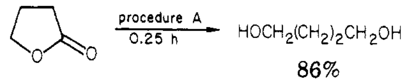
(14)

A diester utilizes four hydrides per molecule of the ester and forms the diol. Thus, diethyl dimethylmalonate reacts rapidly with $LiBH_4$ in ether at 25 °C in 0.25 h, producing the corresponding diol in 83% yield (eq 15).

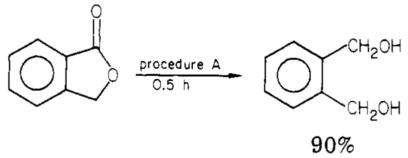


(15)

Lactones are also reduced by the standard procedure, forming diols (eq 16 and 17).



(16)



(17)

Finally, the olefinic ester, ethyl 10-undecenoate, was found to be reduced with concurrent hydroboration, producing a mixture of 1,10- and 1,11-undecane diols (15:85).[13]

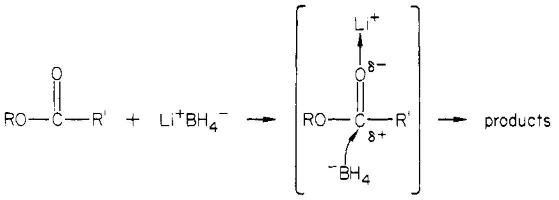
Thus, the present procedure affords a convenient method for the rapid and selective reduction of esters to alcohols.

Discussion

This study reveals significant differences in the reactivities of the metal borohydrides examined ($LiBH_4$, $Ca(BH_4)_2$, $NaBH_4$) for the reduction of esters in various media. In diglyme, a solvent in which all three metal borohydrides are soluble, $LiBH_4$ is the most reactive for the reduction of esters, followed by calcium borohydride, with sodium borohydride being the least reactive. In THF, where $LiBH_4$ and $Ca(BH_4)_2$ can be compared, the observed order of reaction is the same, $LiBH_4 > Ca(BH_4)_2$.

There are two possible effects of the metal ion that would influence the reducing action of the metal borohydride. First, a smaller cation such as lithium would polarize the borohydride anion to a greater extent than a large cation such as sodium. Calcium ion, with its larger charge, should be more polarizing than sodium. However, its greater size could make it less polarizing than lithium.[14] A more polarized borohydride anion is evidently a better source of hydride than a less-polarized anion.[15]

The cation could also influence the reactivity of the ester group.[15] These cations doubtless coordinate with the ester group. Such coordination with the oxygen of the carbonyl group would doubtless increase the electron deficiency of the carbonyl carbon and make it more receptive to the transfer of a hydride moiety from the borohydride anion (eq 18). Again, the ability of the metal ion to coordinate with the carbonyl oxygen would be expected to vary as shown: $Li^+ > Ca^{2+} > Na^+$.



(18)

Both of these facts are in agreement with the observed reactivities in the reduction of esters: $LiBH_4 > Ca(BH_4)_2 > NaBH_4$.

In ethyl ether, the reduction of esters by $LiBH_4$ is much faster than the reductions in THF or DG. We can attribute this to the weaker coordinating power of ethyl ether, as compared to THF and DG. With the lithium ion less strongly solvated, it is in a more effective position to exert its influence, whether by polarizing the borohydride anion or by activating the carboxylic ester grouping.

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[13] Brown, H. C.; Narasimhan, S. *Organometallics* **1982**, *1*, 762.

[14] Cotton, F. A.; Wilkinson, G. "Advanced Inorganic Chemistry"; Wiley: New York, 1967; p 705.

[15] Brown, H. C.; Ichikawa, K. *J. Am. Chem. Soc.* **1961**, *83*, 4372.

On the other hand, an apparent anomaly is observed in protic solvents. In 2-propanol, the reducing effectiveness of $Ca(BH_4)_2$ modestly exceeds that of $LiBH_4$. This could be explained by considering the effect of the metal ion on the coordinating alcohol molecules. The stability of $Ca(BH_4)_2$ in 2-propanol is much lower than that of either $LiBH_4$ or $NaBH_4$ in the same solvent. This may be evidence of the liberation by calcium ion of protons from the coordinated alcohol molecules. Such protons can not only lead to protonolysis of the borohydride anion but may also coordinate with the carbonyl group of esters, thereby enhancing the reactivity of this group to the borohydride anion.

A similar explanation holds good for the reactivity of metal borohydrides in the ethanol medium and would be consistent with the observed parallelism between the instability of a particular metal borohydride in these solvents and its effectiveness for the reduction of esters.

Conclusions

The present data clearly show that lithium borohydride in ethyl ether is a preferred borohydride system for the selective reduction of esters. THF solutions of $LiBH_4$ are less active. However, the modified procedure makes it possible to utilize $LiBH_4$ in ethyl ether, $LiBH_4$ in THF, or $Ca(BH_4)_2$ in THF without a significant disadvantage for any of these three systems. Alcohol solvents are less useful for this application since a considerable amount of the reagent is lost to competitive solvolysis, making it necessary to use excess reagent. The present procedure is highly advantageous since it requires only stoichiometric quantities of the reagent. The reactions are quite rapid, and the product is isolated very easily. A number of selective reductions not readily achievable by lithium aluminum hydride or by sodium borohydride are made possible by this development. Unfortunately, olefinic esters cannot be selectively reduced by borohydride without involvement of the double bond.[13]

Experimental Section

Materials. $LiBH_4$ (95%, Ventron) was used without further purification. $NaBH_4$ (98%, Baker Grade) was used as such. $Ca(BH_4)_2$[7] was prepared using the procedure described elsewhere.[16]

Most of the organic compounds utilized in this study were commercial products of very high purity. However, they were further purified by distillation or recrystallization when necessary. Some compounds were synthesized by using standard procedures.[17] In all of the cases, physical constants agreed well with literature values.

Anhydrous ethyl ether (AR grade, Mallinckrodt) was stored over 5 Å molecular sieves and used. Tetrahydrofuran was distilled over lithium aluminum hydride under nitrogen and stored over 5-Å molecular sieves. Diglyme was purified by the procedure described in the literature.[11] 2-Propanol was purified by distillation after drying over calcium hydride. Absolute ethanol (USP reagent quality) was used as such.

All glassware was dried thoroughly in a drying oven and cooled under a dry steam of nitrogen. All reduction experiments were carried out under a dry nitrogen atmosphere, and hypodermic syringes were used to transfer the solutions.[18]

Preparation of Standard Borohydride Solutions. The typical procedure in ether solvents is as follows. An oven-dried, 250-mL flask containing a magnetic stirrer was flushed with nitrogen, and 3 g of $LiBH_4$ was added under a blanket of nitrogen. The flask was connected to a mercury bubbler, and the system was kept under a positive pressure of nitrogen. Anhydrous ether (100 mL) was added by using a double-ended needle. The contents were stirred overnight. The slurry was transferred to a filter chamber by using a double-ended needle and filtered. The clear solution was concentrated and standardized by analyzing an aliquot with a THF/2 N HCl (1:1) mixture. The concentration of the borohydride solution was found to be 1.35 M.

Similarly, $LiBH_4$ in THF was prepared and standardized (3.35 M). The concentrations of $LiBH_4$ in diglyme and in 2-propanol were found to be 4.25 and 1.46 M, respectively.

In the same way the concentration of $NaBH_4$ in various solvents was determined. The values are given in Table I.

The solution of metal borohydrides in ethanol was prepared in a similar way, but the contents were stirred overnight at 0 °C. The slurry was warmed to 25 °C and quickly filtered. The concentrations obtained are given in Table II. However, since the metal borohydrides react with the solvent (Table III), the solutions were stored at 0 °C and used within 24 h.

Preparation of Standard Calcium Borohydride Solution. A 1000-mL, round-bottomed flask containing a mechanical stirrer and an inlet for nitrogen was equipped with a reflux condenser connected to the nitrogen source through a mercury bubbler. To the predried flask was placed 41.62 g (375 mmol, 0.5 M) of calcium chloride and 90 g of 6-mm-diameter glass beads. Then, 750 mL of tetrahydrofuran was introduced by using a double-ended needle. After the mixture was stirred for some time, 28.37 g (750 mmol, 1.0 M) of sodium borohydride was added to the solution at 25 °C under nitrogen atmosphere. The flask was heated and kept under reflux condition for 1 h. The progress of the reaction was followed by determining the concentration of borohydride by hydrolyzing the clear aliquots of reaction mixture with THF/water/glycerine (1:1:1) solution containing a little HCl. When the reaction was complete, sodium chloride settled down as a white solid. The reaction mixture was centrifuged when a clear solution of calcium borohydride was obtained. The ^{11}B NMR spectrum of the solution showed a quintet centered at −36.6 ppm, with respect to the $BF_3 \cdot OEt_2$. The solution was transferred by using a double-ended needle into a 1000-mL, round-bottomed flask and concentrated under reduced pressure. The borohydride concentration was determined as before to be 3.09 M.

About 30 mL of this solution was used for isolating $Ca(BH_4)_2$ free from the solvent of crystallization. Solutions of $Ca(BH_4)_2$ in other solvents were prepared as described before.[16]

Procedure for the Rate Study. The reduction of ethyl caproate by $LiBH_4$ in ether is representative. An oven-dried, 50-mL flask containing a side arm and magnetic stirrer was cooled under nitrogen and connected to the mercury bubbler. To the flask was added $LiBH_4$ in ether (3.7 mL, 1.35 M, 5 mmol) followed by 0.5 mL of ether. Ethyl caproate (0.82 mL, 5 mmol) was injected into the flask. The resulting solution contained 1.0 M borohydride and 1.0 M ester. Aliquots (0.25 mL) were withdrawn at various time intervals and analyzed by hydrolysis as before. A blank experiment was performed in which ether was substituted for the ester. From the difference, the number of millimoles of hydride used for reduction per millimole of ester and hence the percentage of reaction was calculated. The experiment was repeated for concordance.

The rates of reaction in other cases were followed in a similar manner, maintaining identical concentrations of borohydride and ester.

In the case of rate studies at reflux temperature, the above procedure was repeated in a flask equipped with a reflux condenser. The results are given in Tables IV and V.

In the case of reactions of heterogeneous nature, the rate was followed by conducting the experiment under identical conditions in several flasks and hydrolyzing the whole mixture to obtain the residual hydride concentration.

Procedure for the Reduction of Ester. Procedure A. The reduction of ethyl benzoate by lithium borohydride in ether is representative (procedure A). In a typical experiment, a 50-mL, round-bottomed flask containing a magnetic stirring bar and an inlet for nitrogen was equipped with a distillation setup. The receiver end was connected to a mercury bubbler. The whole system was flushed with nitrogen and maintained under a positive pressure of nitrogen. To the flask was added 10.2 mL (1.35 M, 13.75 mmol) of lithium borohydride in ether, and 3.6 mL (25 mmol) of ethyl benzoate was introduced into the flask by using

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[16] Brown, H. C.; Choi, Y. M.; Narasimhan, S. *Inorg. Chem.* **1981**, *20*, 4454.

[17] Fieser, L. F.; Fieser, M. "Reagents for Organic Synthesis"; Wiley: New York, 1967; p 705.

[18] For complete details on this technique see ref 12.

a syringe. The solution was stirred, and 4 mL of toluene was added to it. The reaction flask was heated on an oil bath. The rate of heating was maintained such that it reached 95–100 °C in 15–20 min. The solvent ether which distilled off was collected in the measuring cylinder. Generally the recovery of solvent was more than 95% in about 15 min. Toluene controls the bumping of the residue when the last traces of ether were distilling by keeping it in the fluid state. The temperature was maintained at 100 °C for the entire reaction period. The completion of the reaction was tested by hydrolyzing the whole residue with dilute H_2SO_4, extracting the organic components in ether, and analyzing the dry ether layer by GLC (CW-20M, 6 ft × $^1/_8$ in. column). The authentic sample was used for identification of the ester. The absence of any peak corresponding to the ester in GLC indicated the completion of the reaction. The whole procedure was repeated until completion of the reaction. Normally, the analysis was done at 0.25, 0.5, 1.0, 2.0 h, etc.

For isolation of the product, the experiment was repeated, and after the appropriate time interval necessary for the completion of the reaction, the receiver end was connected to an aspirator pump, the reaction flask still being immersed in the oil bath. Toluene distilled off in 5 min. The oil bath was removed, and the flask was heated by using a hot air blower (~5 min) to ensure complete removal of toluene. The borate complex was then hydrolyzed to give the products.

The hydrolysis was effected with 15–20 mL of water containing a sufficient amount of acid (2.5 mL of 6 N HCl) for neutralization. The mixture was stirred for some time, and anhydrous K_2CO_3 was added to saturate the aqueous layer. The liberated alcohol was extracted with portions (3 × 10 mL) of ether. The ether layer was separated by using a double-ended needle. Finally, a small portion of ether (5 mL) was added, and the ether layer separated by using a separating funnel. The combined ether extract was dried over anhydrous K_2CO_3 and concentrated. Fractional distillation provided 2.43 g (90%) of pure benzyl alcohol: bp 96–98 °C (15 mm) [lit.[3] 93 °C (10 mm)]; ^{1}H NMR (neat) δ 4.7 (s, 2 H, CH_2), 5.6 (s, 1 H, OH), 7.3–7.4 (s, 5 H, aromatic protons); n^{20}_{D} 1.5391 (lit.[3] n^{20}_{D} 1.5396).

Reduction of Ethyl Caproate. The general procedure was followed, and 2.20 g (86%) of 1-hexanol was obtained: bp 80 ° (15 mm) [lit.[19] bp 158 °C (760 mm)]; ^{1}H NMR (neat) δ 0.8 (t, 3 H, CH_3), 1–1.8 (m, 8 H, 4 CH_2), 3.3–3.6 (t, 2 H, OCH_2), 5.1 (t, 1 H, OH); n^{20}_{D} 1.4175 (lit.[19] n^{20}_{D} 0.4178).

Reduction of Ethyl Phenylacetate. The reduction of ethyl phenylacetate produced 2.81 g (92%) of 2-phenylethanol: bp 106–107 °C (15 mm) [lit.[20] bp 99–100 °C (10 mm)]; ^{1}H NMR (neat) δ 2.9–3.3 (t, 2 H, OCH_2), 3.8–4.2 (t, 2 H, CH_2), 5.0–5.1 (s, 1 H, OH), 7.4–7.6 (s, 5 H, aromatic protons); n^{20}_{D} 1.5270 (lit.[20] n^{20}_{D} 1.526).

Reduction of Ethyl Cyclohexanecarboxylate. Cyclohexylcarbinol was produced: 2.59 g (91%); bp 84–86 °C (15 mm) [lit.[21] bp 83 °C (14 mm)]; ^{1}H NMR (neat) δ 0.5–2 (m, 10 H, $(CH_2)_5$), 2.5 (s, 1 H, H), 3.2–3.5 (t, 2 H, OCH_2), 5.0–5.2 (t, 1 H, OH); n^{20}_{D} 1.4635 (lit.[21] n^{20}_{D} 1.4640).

Reduction of Ethyl Adamantane-1-carboxylate. The procedure was as before. The ether extract produced on removal of ether 3.98 g (96%) of adamantane-1-methanol: mp 115–117 °C (lit.[22] mp 115–118 °C); ^{1}H NMR ($CDCl_3$) δ 1.5–1.7 (d, 12 H, 6 CH_2), 1.9–2.2 (s, 3 H, 3 CH), 3.0–3.2 (s, 2 H, OCH_2), 3.49 (s, 1 H, OH).

Reduction of Ethyl *p*-Chlorobenzoate. Reduction produced 3.40 g of *p*-chlorobenzyl alcohol in a yield of 95%. Recrystallization from hot water produced 3.20 g (90%) of pure alcohol: mp 70–72 °C (lit.[7] mp 70–72 °C); ^{1}H NMR ($CDCl_3$) δ 1.89 (s, 1 H, OH), 4.60 (s, 2 H, CH_2), 7.22 (s, 4 H, aromatic protons).

Reduction of Ethyl *m*-Bromobenzoate. *m*-Bromobenzyl alcohol was isolated: 4.40 g (94%); bp 84–85 °C (0.15 mm) [lit.[23] bp 165 °C (16 mm)]; ^{1}H NMR ($CDCl_3$) δ 3.5 (s, 1 H, OH), 4.4 (s, 2 H, CH_2), 6.95–7.45 (m, 4 H, aromatic protons); n^{20}_{D} 1.5810 (lit.[23] n^{20}_{D} 1.5847).

Reduction of Ethyl Trichloroacetate. The reduction was carried out at room temperature. Hence, toluene was not added to the reaction mixture. The product was isolated as before. 2,2,2-Trichloroethanol was obtained: 3.00 g (80%); bp 150 °C (lit.[3] bp 151 °C); ^{1}H NMR ($CDCl_3$) δ 4.2 (s, 2 H, CH_2), 4.4–4.7 (s, 1 H, OH); n^{20}_{D} 1.4883 (lit.[3] n^{20}_{D} 1.4885).

Reduction of Ethyl *p*-Nitrobenzoate. The procedure was the same except that reverse addition of reagents was employed. The reaction solution was yellow initially and turned brown when the reaction was complete. The isolation procedure was as usual. The product upon recrystallization from hot water produced 2.67 g (70%) of pure *p*-nitrobenzyl alcohol: bp 92–93 °C (lit.[7] bp 93 °C); ^{1}H NMR ($CDCl_3$) δ 2.23 (s, 1 H, OH), 4.8 (s, 2 H, CH_2), 7.36–8.30 (q, 4 H, aromatic protons).

Reduction of Ethyl *m*-Cyanobenzoate. The reaction mixture was initially yellow and turned deep brown when the reaction was complete. *m*-Cyanobenzyl alcohol was isolated as before; yield 2.07 g (62%); bp 109–110 °C (0.1 mm); ^{1}H NMR ($CDCl_3$) δ 3.74 (s, 1 H, OH), 4.62 (s, 2 H, CH_2), 7.13–7.65 (m, 4 H, aromatic protons); $n^{28.5}_{\mathrm{D}}$ 1.5502.

Reduction of Ethyl *m*-Methoxybenzoate. Pure *m*-methoxybenzyl alcohol was isolated: 3.30 g (95%); bp 78–79 °C (0.13 mm) [lit.[24] bp 250 °C (723 mm)]; ^{1}H NMR ($CDCl_3$) δ 2.86 (t, 1 H, OH), 3.73 (s, 3 H, OCH_3), 4.52 (d, 2 H, CH_2), 6.60–7.35 (m, 4 H, aromatic protons); n^{25}_{D} 1.5433 (lit.[24] n^{20}_{D} 1.5440).

Reduction of Ethyl *p*-Methoxybenzoate. Reduction produced 3.33 g (96%) of *p*-methoxybenzyl alcohol: bp 80–82 °C (0.7 mm) [lit.[25] bp 257 °C (760 mm)]; ^{1}H NMR ($CDCl_3$) δ 2.80 (t, 1 H, OH), 3.73 (s, 3 H, OCH_3), 4.49 (d, 2 H, CH_2), 6.65–7.36 (q, 4 H, aromatic protons); n^{25}_{D} 1.5437 (lit.[25] n^{25}_{D} 1.5420).

Reduction of γ-Butyrolactone. The reduction procedure was the same as before. However, the product was extracted by using tetrahydrofuran instead of ether. Fractional distillation produced 1.90 g n86%) of 1,4-butanediol: bp 130–132 °C (15 mm) [lit.[26] bp 235 °C (760 mm)]; ^{1}H NMR ($CDCl_3$) δ 1.5–1.9 (s, 4 H, $2CH_2$), 3.5–3.9 (s, 4 H, 2-OCH_2), 5.4–5.6 (s, 2 H, 2-OH); n^{20}_{D} 1.4468 (lit.[26] n^{20}_{D} 1.4467).

Reduction of Phthalide. The procedure was similar to the reduction of ethyl *p*-nitrobenzoate. Phthalyl alcohol was extracted by using tetrahydrofuran. Removal of the solvent and recrystallization from ether produced 3.10 g (90%) of phthalyl alcohol: mp 64–65 °C (lit.[27] mp 64–65 °C); ^{1}H NMR ($CDCl_3$) δ 4.0 (s, 2 H, 2-OH), 4.6 (s, 4 H, 2 CH_2), 7.2 (s, 4 H, aromatic protons).

Reduction of Diethyl Dimethylmalonate. The reduction procedure was similar to ethyl trichloroacetate. The amount of ester taken was 12.5 mmol since it contains two carboxylate groups. The product was extracted by using tetrahydrofuran. 2,2-Dimethyl-1,3-propanediol was obtained: 1.082 g (83%); mp 122–126 °C (lit.[28] mp 123–127 °C); ^{1}H NMR ($CDCl_3$) δ 0.94 (s, 6 H, $2CH_3$), 3.43–3.7 (d, 6 H, $2CH_2$, and 2-OH).

Acknowledgment. We thank the U.S. Army Research Office for financial support.

Registry No. $LiBH_4$, 16949-15-8; $NaBH_4$, 16940-66-2; $Ca(BH_4)_2$, 17068-95-0; $CCl_3COOC_2H_5$, 515-84-4; ethyl benzoate, 93-89-0; ethyl caproate, 123-66-0; ethyl cyclohexanecarboxylate, 3289-28-9; ethyl adamantanecarboxylate, 2094-73-7; ethyl phenylacetate, 101-97-3; ethyl *p*-chlorobenzoate, 7335-27-5; ethyl *m*-bromobenzoate, 24398-88-7; ethyl *p*-nitrobenzoate, 99-77-4; ethyl *m*-cyanobenzoate, 2463-16-3; ethyl *p*-methoxybenzoate, 94-30-4; ethyl *m*-methoxybenzoate, 10259-22-0; diethyl dimethylpropanedioate, 1619-62-1; 2(3*H*)-dihydrofuranone, 96-48-0; 1(3*H*)-isobenzofuranone, 87-41-2; *m*-cyanobenzyl alcohol, 874-97-5.

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