2,2,4,4-Tetramethyl-3-methylenecyclobutanone (17).—A mixture of 9 (1.70 g, 10 mmol) and triphenylphosphine (2.62 g, 10 mmol) in 20 ml of dry benzene was refluxed for 38 hr. The reaction mixture was periodically examined by glpc. The reaction was found to be about 50% complete after 3 hr and about 90% complete after 38 hr. The reaction proceeded cleanly to give only triphenylphosphine sulfide and **17**; no other products were found by glpc.

Samples of **17** (mp 42.5–44°) were collected from an analytical chromatograph in capillary tubes. The following spectral data[24] were obtained: ir (CCl_4) 3050, 2940, 1790, 1675, 1460, 1000, and 890 cm^{-1}; uv λ_{max}^{hexane} 211 nm (ϵ 1800) and 313 (22); nmr (CCl_4) δ 5.03 (singlet) and 1.22 ppm (singlet) with area ratio 1:6. The mass spectrum showed the mass of the parent ion to be 138.

A 2,4-dinitrophenylhydrazone of **17** was prepared, mp 145–147°; uv $\lambda_{max}^{abs\ EtOH}$ 212 nm (ϵ 6510), 230 (6360), and 355 (10,300).

Anal. Calcd for $C_{15}H_{18}N_4O_4$: C, 56.60; H, 5.70; N, 17.60. Found: C, 56.81; H, 5.73; N, 17.58.

4,4,6,6-Tetramethyl-1-thiaspiro[2.3]hexan-5-yl Acetate (15).—The mixture of *cis* and *trans* alcohols **12** (0.5 g, 2.9 mmol) was heated with 0.5 g of sodium acetate and 5 ml of acetic anhydride on a steam bath for 2 hr. The solution was then poured into 30 ml of cold water. The mixture was allowed to stand, with occasional stirring, for 30 min. The aqueous mixture was extracted with three 20-ml portions of ether, and the combined ether extracts were washed with cold 15% sodium carbonate. The ether layer was dried over anhydrous sodium sulfate, filtered, and evaporated to give 0.54 g (87%) of a white solid. The mixture of *cis* and *trans* acetates was recrystallized from 30–60° petroleum ether, mp 35–37.5°.

The following spectral data were obtained for **15**: ir (KBr) 2960, 1740, 1460, 1450, 1365, 1230, and 1050 cm^{-1}; the nmr ($CDCl_3$) of the major isomer showed absorption at δ 4.60 (AcOCH), 2.46 (CH_2), 2.10 (CH_3CO_2), 1.12 (CH_3), and 1.07 ppm (CH_3); the minor isomer displayed corresponding absorptions at δ 4.74, 2.40, 2.10, 1.18, and 0.98 ppm. All peaks in the nmr spectrum were singlets, and the spectrum showed that the sample was a 30:70 mixture. A high-resolution mass spectrum of the mixture gave the measured mass of the parent ion as 214.1032, which corresponds to the molecular formula $C_{11}H_{18}O_2S$ (calcd for $C_{11}H_{18}O_2S$: 214.1027).

Reaction of Thiirane 9 with Raney Nickel.—Thiirane **9** (1.0 g, 5.9 mmol) was dissolved in 25 ml of ethyl alcohol and Raney nickel catalyst (~10 g) was added. The reaction mixture became warm. The mixture was refluxed under nitrogen for 3 hr and then filtered through Celite filter aid.

The filtrate was examined by glpc. A major product and a minor product were found. These two products were collected from the analytical glpc in capillary tubes. The minor product was shown to have structure **17** by comparison of its infrared spectrum with that of an authentic sample.

The major product, 2,2,3,4,4-pentamethylcyclobutanone (**16**), was isolated as a colorlessl iquid. The following spectral data were obtained for **16**: ir (neat) 2950, 1785, 1580, 1380, 1 365, and 1040 cm^{-1}; nmr ($CDCl_3$) δ 1.97 (quartet, $CHCH_3$, J = 7 cps), 1.17 (singlet, CH_3), 1.06 (singlet, CH_3), and 1.03 ppm (doublet, $CHCH_3$, J = 7 cps) [lit.[25] nmr (CCl_4) δ 1.91, 1.15, 1.06, and 1.06 ppm]; uv λ_{max}^{hexane} 311 nm (ϵ 23), [lit.[20] uv λ_{max}^{hexane} 311 nmr (ϵ 22)]. The mass spectrum of **16** showed the mass of the parent ion to be 140.

A 2,4-dinitrophenylhydrazone of **16** was prepared, mp 144–145° (lit.[20] mp 145°).

Registry No.—**8a**, 23604-61-7; **9**, 23604-62-8; **11**, 23604-63-9; *cis*-**12**, 23601-92-5; *trans*-**12**, 23601-93-6; *cis*-**15**, 23601-94-7; *trans*-**15**, 23601-95-8; **17**, 20019-11-8; 2,4-dinitrophenylhydrazone of **17**, 23604-65-1.

Acknowledgment.—The author is grateful to Dr. V. W. Goodlett and Mr. H. D. Kinder, Research Laboratories, Tennessee Eastman Co., for helpful discussions of the nmr spectra.

(24) The spectral data agree favorably with those reported by Hamon.[17]

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The Facilitation of Sodium Borohydride Reduction of Esters of Phenols and of Acidic Alcohols

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The reduction of esters (RCOOR') by sodium borohydride is facilitated by use of R' groups more electronegative than methyl, rate enhancements of at least 300-fold having been demonstrated. The rates of reduction of substituted phenyl esters correlate linearly with the pK_a values of the corresponding phenols (ρ = 2.6), a separate correlation being obtained for alcohols. In 1,2-dimethoxyethane as solvent, esters of acidic alcohols are 10–50 times as reactive toward borohydride as are those of phenols of comparable pK_a, the difference being ascribed to conformational or steric obstruction by the aromatic ring; furthermore, reduction is significantly faster in media containing water. By use of an appropriate alcohol for esterification, carboxyl groups can be reduced selectively to primary alcohols in the presence of functional groups which are reactive toward more powerful reducing agents.

Esters of simple carboxylic acids are normally resistant to reduction by sodium borohydride.[2] However, reduction can sometimes be effected by activation of the reagent, *e.g.*, by its conversion, *in situ*, into lithium or magnesium borohydride,[3] or to a more reactive alkoxyborohydride.[4]

In connection with studies on the selective modification of proteins,[5] we encountered the problem of effecting the specific reduction of esters under the mildest possible conditions. Since lithium borohydride[6a] and diborane[5,6b] are known to reduce amides as well as esters, and since the solubility and stability properties of proteins restrict the use of the methods cited above, an alternative mode of reduction was sought.

In a number of instances, sodium borohydride has been effective in reducing esters of carboxylic acids con-

(1) Associate in the Visiting Program, National Institutes of Health, 1967–1969.

(2) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, Inc., New York, N. Y., 1965, Chapter 2.

(3) H. C. Brown, E. J. Mead, and B. C. Subba Rao, *J. Amer. Chem. Soc.*, **77**, 6209 (1955).

(4) (a) H. C. Brown and E. J. Mead, *ibid.*, **75**, 6263 (1953); (b) H. C. Brown, E. J. Mead, and C. J. Shoaf, *ibid.*, **78**, 3616 (1956); (c) M. S. Brown and H. Rapoport, *J. Org. Chem.*, **28**, 3261 (1963).

(5) See, *e.g.*, S. Takahashi and L. A. Cohen, *Biochemistry*, **8**, 864 (1969).

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TABLE I

ESTERS OF 3-PHENYLPROPIONIC ACID[a]

Ester	Registry no.	Mp or bp, °C (mm)	Ester	Registry no.	Mp or bp, °C
Methyl	103-25-3	75 (1)	*p*-Fluorophenyl (B)	23522-72-7	29–34
Propargyl	23522-64-7	120 (2)	*p*-Chlorophenyl (D)	23522-73-8	48–49
Trichloroethyl	23522-65-8	138–140 (1.5)	*m*-Chlorophenyl (B)	23522-74-9	34
Trifluoroethyl	23522-66-9	69–72 (1)	Pentachlorophenyl (E)	23522-75-0	106–107
Hexafluoroisopropyl	23522-67-0	61–62 (1)	*p*-Bromophenyl (C)	23522-76-1	54–55
3,5-Dinitrobenzyl (A)[b]	23568-84-5	83–84	*p*-Iodophenyl (C)	23522-77-2	64–67
Phenyl	726-26-1	147 (1)	*p*-Nitrophenyl (E)	17895-71-5	94–95
p-Methylphenyl (B)	22020-95-7	35–36	*m*-Nitrophenyl (C)	23522-79-4	63–64
p-*t*-Butylphenyl (B)	23522-70-5	49–50	2,4-Dinitrophenyl (C)	23522-80-7	54–55
p-Methoxyphenyl (C)	23522-71-6	40			

[a] All compounds provided acceptable elemental analyses. [b] Solvents for recrystallization: A, chloroform; B, petroleum ether; C, ethyl acetate–petroleum ether; D, cyclohexane; E, ethyl acetate.

taining electron-withdrawing substituents α to the carbonyl group.[7] Indeed, a correlation of the rate of ester reduction with the electron-withdrawing power of the substituent has been demonstrated,[7e] although intramolecular complexing with the reagent may become an accessory factor.[7c] Such observations led us to consider an alternative route to activating the carbonyl group, *i.e.*, by utilizing the esters of phenols and of alcohols more acidic than methanol. Although thiol esters[8a] and carbonic anhydrides[8b] are reduced readily by sodium borohydride, the meager data available provide little basis for estimating the dependence of reduction rate of an ester on the acidity of the corresponding alcohol or phenol. We have, therefore, determined the rates of reduction of a series of esters of 3-phenylpropionic acid and have found a linear variation of the logarithm of the rate with the pK_a of alcohol or phenol. Furthermore, esters of alcohols are significantly more reactive toward borohydride than are those of phenols of comparable pK_a. Rates of reduction greater than 300 times that of the methyl ester have been observed.

Results

Esters of 3-phenylpropionic acid were chosen for the present study because of their ease of purification and because the reduction product, 3-phenyl-1-propanol, is readily separated from other components by gas–liquid chromatography. Since the pK_a value of 3-phenylpropionic acid (4.66)[9] is similar to those of simple aliphatic carboxylic acids, the observed rates of reduction are probably applicable to the corresponding esters of a variety of carboxylic acids. Initially, attempts were made to utilize esters of cinnamic acid, since rates of reduction could be followed spectrophotometrically. However, saturation of the double bond appeared to be competitive with ester reduction for such compounds.[4c]

The phenols and alcohols used in this study were chosen to provide as wide a range of pK_a values as possible. However, for phenols having pK_a values below 9, rates of reduction were too fast to provide reliable data. The esters of 3-phenylpropionic acid (Table I) were obtained in yields of 60–90% by coupling the acid and the hydroxyl compound by means of trifluoroacetic anhydride.[10] In order to avoid wide alterations in the nature of the reagent, 1,2-dimethoxyethane was used as solvent at 40°. At this temperature, a solution saturated with sodium borohydride was found to be 0.11 *M* (manometric assay). The amount of sodium borohydride added in each run corresponded to a 10–20 molar excess of reagent, a portion remaining undissolved.

Reaction rates were obtained by assay of the 3-phenyl-1-propanol content of aliquots on a glpc column. For all esters studied, pseudo-first-order kinetics were observed up to 50–80% reaction (Table II). Some representative results are shown in Figure 1. In a few cases, small deviations occurred beyond 50% conversion. Fivefold variations in the initial concentration of ester or in the ester/borohydride ratio had no signifi-

TABLE II

RATES OF BOROHYDRIDE REDUCTION OF ESTERS OF 3-PHENYLPROPIONIC ACID (RCOOR′)

R′	pK_a(R′OH)[a]	σ[b]	$k' \times 10^4$, min^{-1}
m-Chlorophenyl	9.02[c]	0.40	500
p-Iodophenyl	9.30	0.28	230
p-Bromophenyl	9.36	0.25	200
p-Chlorophenyl	9.42	0.22	162
p-Fluorophenyl	9.91	0.01	48.0
Phenyl	9.99	0	39.8
p-*t*-Butylphenyl	10.23[d]	−0.14	20.8
p-Methylphenyl	10.26	−0.15	17.4
p-Methoxyphenyl	10.21	−0.13	7.85
Hexafluoroisopropyl	9.30[e]		(1070)[f]
Trifluoroethyl	12.37[g]		35.6
Trichloroethyl	12.70[h]		13.6
Propargyl	13.55[g]		9.40
Methyl	15.09[i]		1.52

[a] Unless indicated otherwise, pK_a values are taken from A. I. Biggs and R. A. Robinson, *J. Chem. Soc.*, 388 (1961). [b] Values based on the ionization of phenols, calculated from the equation $pK_a = 9.919 - 2.229\sigma$ (A. I. Biggs and R. A. Robinson, *J. Chem. Soc.*, 388 (1961). [c] C. M. Judson and M. Kilpatrick, *J. Amer. Chem. Soc.*, **71**, 3110 (1949). [d] L. A. Cohen and W. M. Jones, *ibid.*, **85**, 3397 (1963). [e] B. L. Dyatkin, E. P. Mochalina, and I. L. Knunyants, *Tetrahedron*, **21**, 2991 (1965). [f] Extrapolated from Figure 2, using the pK_a value of 9.30. [g] P. Ballinger and F. A. Long, *J. Amer. Chem. Soc.*, **82**, 795 (1960). [h] S. Takahashi and L. A. Cohen, manuscript in preparation. [i] J. Murto, *Acta Chem. Scand.*, **18**, 1043 (1964).

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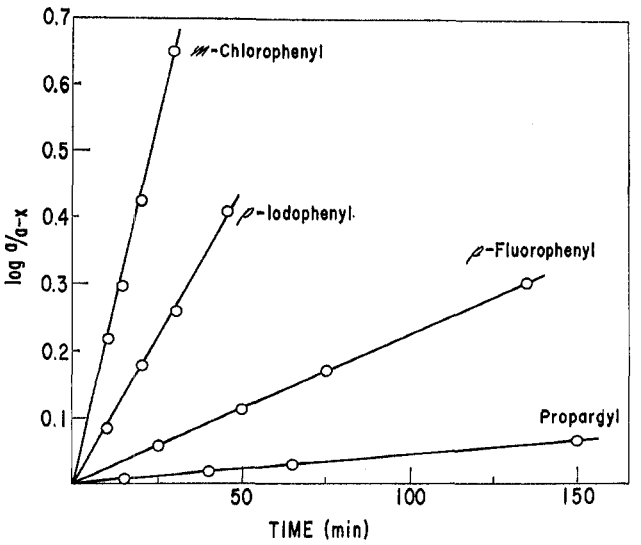

Figure 1.—Representative pseudo-first-order plots of the reduction of esters of 3-phenylpropionic acid with sodium borohydride in 1,2-dimethoxyethane at 40°.

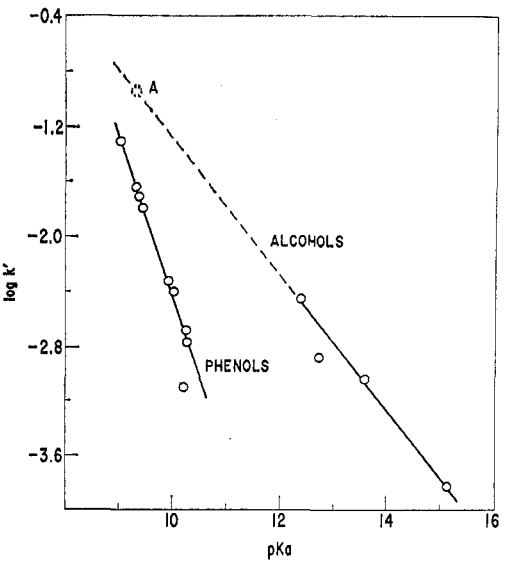

Figure 2.—Plots of log k' (borohydride reduction of esters) *vs.* pK_a of phenol or alcohol component of ester: A, extrapolated rate for hexafluoroisopropyl ester, based on pK_a of 9.30.

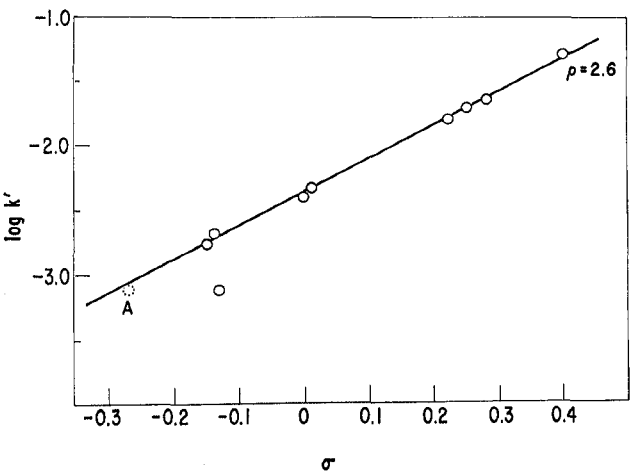

Figure 3.—Plot of log k' (borohydride reduction of esters) *vs.* σ values of aryl substituents: A, correlation of *p*-methoxy substituent, using a σ value of −0.27.

cant effect on values of k'. In the cases of *p*-nitrophenyl, 2,4-dinitrophenyl, pentachlorophenyl, and hexafluoroisopropyl esters, reduction was too rapid to obtain reliable kinetic data by this technique, even at temperatures below 40°. Thin layer chromatography was used to demonstrate the complete conversion of these esters into 3-phenyl-1-propanol within 5 min of mixing. Reduction of the 3,5-dinitrobenzyl ester was complicated by the formation of intensely colored complexes with sodium borohydride, probably owing to proton abstraction from the benzene ring. Similarly colored species are formed by the addition of sodium borohydride or of strong nonreducing bases to solutions of *m*-dinitrobenzene.

Solvent effects were examined briefly by comparing the rates of reduction of the phenyl ester at 0° in 1,2-dimethoxyethane ($k' = 0.53 \times 10^{-3}$ min^{-1}) and in dimethoxyethane–water (7:3, v/v) ($k' = 4.10 \times 10^{-3}$ min^{-1}). Thus reduction is 7.5 times as rapid in the presence of water, at least for the one case examined.[11] Satisfactory comparisons could not be made for the more reactive esters because of the rapidity of reduction and the competitive alkaline hydrolysis of such esters.

As is evident from Figure 2, log k' varies linearly with the pK_a of the phenol component of the phenyl ester ($\log k' = -1.15pK_a + 9.05$). A similar plot of log k' *vs.* σ (Figure 3) provides a ρ value of 2.6. The reason for the deviation of the *p*-methoxyphenyl ester is not immediately obvious, being well beyond the limits of experimental error. It is interesting, although probably fortuitous, that a correlation with the Hammett plot of Figure 3 can be obtained by use of the σ value (−0.27) based on ionization of *p*-anisic acid rather than that for ionization of *p*-methoxyphenol (−0.13).

Studies with esters of alcohols were limited by the unavailability of sufficiently acidic alcohols. Thus a wide gap exists between trifluoroethanol (pK_a 12.37) and hexafluoro-2-propanol (pK_a 9.3). From the limited data obtained, it would appear that a linear relationship does, in fact, exist between the logarithm of the rate of ester reduction and the pK_a of the corresponding alcohol. From three points, the equation $\log k' = -0.50pK_a + 3.73$ may be derived. Despite the use of a revised value for the pK_a of trichloroethanol,[12] the rate of reduction of the trichloroethyl ester was less than that required for linear correlation, possibly owing to steric interaction between the substituent and the borohydride–carbonyl complex.[12]

Discussion

The inductive effect of a substituent on the β carbon of ethyl alcohol influences the acidity of the alcohol in a predictable manner, which can be related to the Taft constant for that substituent.[13a] It is reasonable to expect the inductive effect to be relayed to the adjacent

(11) The enhanced reactivity of sodium borohydride, or of its hydrolysis products, in aqueous media has been noted previously: H. C. Brown and K. Ichikawa, *J. Amer. Chem. Soc.*, **83**, 4372 (1961); see also ref 7e.

(12) S. Takahashi and L. A. Cohen, manuscript in preparation. Although partial dehalogenation of the trichloromethyl substituent by borohydride was considered, glc demonstrated the absence of any abnormal reduction products.

(13) (a) P. Ballinger and F. A. Long, *J. Amer. Chem. Soc.*, **82**, 795 (1960); (b) T. C. Bruice, T. H. Fife, J. J. Bruno, and N. E. Brandon, *Biochemistry*, **1**, 7 (1962).

carbonyl carbon in the corresponding ester, thus determining its relative electrophilicity toward borohydride. Similarly, the combined inductive and resonance effects of a substituent on the benzene ring, acting on the phenolic oxygen, should be transmitted to the adjacent carbonyl group as a net inductive effect.[13b] The correlation of reduction rate with pK_a, in both series, is in accord with such considerations. On the other hand, esters of 3-phenylpropionic acid with alcohols are reduced significantly faster than are those with phenols of comparable acidity. Whereas the ester of *p*-iodophenol (pK_a 9.3) shows $t_{1/2}$ = 30 min, $t_{1/2}$ for the ester of hexafluoro-2-propanol (pK_a 9.3) is probably less than 3 min. Furthermore, the trifluoroethyl ester was reduced at approximately the same rate as the phenyl ester, despite a pK_a difference of 2.4 units.

In earlier studies on alkaline hydrolysis,[13b] esters of phenols have been found, invariably, to be more reactive than those of alcohols of comparable pK_a, phenyl acetate hydrolyzing six times as rapidly as trifluoroethyl acetate. Such results are in accord with electronic considerations. Furthermore, the rates of alkaline hydrolysis of both types of esters can be correlated with the pK_a of the leaving group on a single plot.[13b] Since attack of hydride or of borohydride ion on the ester carbonyl may be viewed as another example of a nucleophilic reaction, it is doubtful whether the present results can be explained on the basis of electronic factors alone. Inspection of molecular models reveals that phenyl esters cannot achieve the *trans* conformation of simple aliphatic esters. Indeed, it has been concluded from molecular polarizability measurements that the carbonyl group of a phenyl ester is perpendicular to the aromatic plane.[14] Such a difference in conformation may force the borohydride ion to approach the carbonyl group of a phenyl ester from a less favorable direction than is possible for an aliphatic ester. Alternatively, the bulk of the aromatic ring may present a steric obstacle to the formation either of the borohydride–carbonyl complex or of the tetrahedral alkoxyborohydride intermediate. The importance of such factors is difficult to evaluate, since the electronic and steric components are not readily separated. We studied the reduction of the hexafluoroisopropyl ester, as the closest aliphatic approximation to a phenyl ester, both in steric and in electronic properties. As previously noted, the rate proved to be too fast to be measured accurately.

The rates of borohydride reduction of substituted phenyl esters are considerably more sensitive to the nature of the substituent (ρ = 2.6) than are those for alkaline hydrolysis of phenyl acetates (ρ = 0.8).[15] Because of the sizable differences in sensitivity to substitution, both in alcohols and in phenols, rough comparisons reveal that $k_2^{OH^-}/k^{BH_4^-}$ = *ca.* 1000 for the trifluoroethyl ester, 100 for the phenyl ester, and only 3 for the *p*-nitrophenyl ester. Therefore, in the application of borohydride reduction of activated esters in aqueous media, it is desirable to employ high concentrations of reducing agent at as low an alkaline pH as is practical.

Thus it is evident that sodium borohydride reduction of simple carboxylic acids can be achieved under mild conditions by prior esterification with an appropriate partner. The rate data, considered together with stability of the ester in mildly alkaline media,[13b] suggest the choice of the trifluoroethyl ester, particularly for the carboxyl groups of peptides and proteins. Its candidacy is supported by the relative ease of esterification of carboxylic acids with trifluorodiazoethane.[16]

Experimental Section[17]

Preparation of Esters of 3-Phenylpropionic Acid.—To a solution of 0.02 mol of 3-phenylpropionic acid in an equimolar amount of trifluoroacetic anhydride was added 0.02 mol of alcohol or phenol, and the reaction mixture was stored at ambient temperature for 3 hr.[10] In several instances, the product separated as a solid during the reaction. In the case of 2,4-dinitrophenol, esterification was performed at 40° for 3 hr, and in that of pentachlorophenol, at 40° for 5 hr. The reaction mixture was poured into aqueous sodium bicarbonate with vigorous stirring and cooling. Solid esters were collected by filtration, washed with water, and dried over KOH *in vacuo;* solvents for recrystallization are listed in Table I. Liquid esters were extracted with ether, and the extracts were washed with 3% sodium bicarbonate, dried (Na_2SO_4), and evaporated. The residual oils were purified by distillation at reduced pressure. Alternatively, the esters were distilled directly from the esterification reaction mixture. The purified esters were obtained in yields of 60–90%. Physical and analytical data are summarized in Table I.

Kinetic Measurements.—A solution of ester in 1,2-dimethoxyethane (30–40 ml, 0.1–0.02 *M*) was placed in a jacketed test tube maintained at 40 ± 0.1° with a circulating water bath. Solid sodium borohydride (1–2 g) was added in one portion and the reaction mixture was stirred vigorously with a magnetic stirrer. At appropriate time intervals, 5-ml aliquots were removed for assay of 3-phenyl-1-propanol. To each aliquot was added, with cooling, 1.5 ml of 6 *N* hydrochloric acid to destroy excess borohydride. After 30 min, the solution was made alkaline with 2.5 ml of 6 *N* sodium hydroxide and the phases were then separated. The aqueous phase was extracted with three portions of 4 ml of ethyl acetate and the combined organic extracts were evaporated to dryness. The residue was diluted to 0.5 or 1 ml with ethyl acetate and a measured amount of 1-decanol was added to serve as an internal standard for gas chromatography. Analyses were performed on a Glowall, Unilab Model 400, gas chromatograph using a column of Gas-Chrom P (HMDS) coated with 20% Reoplex 400 (Applied Science Labs, Inc.). At a column temperature of 175° and a flash temperature of 220°, 3-phenyl-1-propanol emerged at 9–10 min, well separated from other reaction components. Peak areas were integrated and compared with a standard calibration curve. Conversion yields used for rate calculations were the averages of at least three glpc determinations, maximum deviations falling within 5%. When the identical manipulations were performed on control samples of 3-phenyl-1-propanol, recoveries of 96–100% were obtained. The retention times of *p*-fluorophenol and of *p*-cresol were sufficiently close to that of 3-phenyl-1-propanol to cause peak distortion. Since the corresponding anisoles did not interfere in the gas chromatographic analysis, the reaction mixtures containing these phenols were treated with a large excess of ethereal diazomethane for 24 hr prior to analysis; under these conditions, methylation of the phenols appeared to be complete.

Registry No.—Sodium borohydride, 16940-66-2.

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(16) B. L. Dyatkin and E. P. Mochalina, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1225 (1964).

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