Esterification Kinetics of 5-Hydroxy-1,3-dioxane Derivatives with Acid Anhydrides and Acid Chlorides in Pyridine

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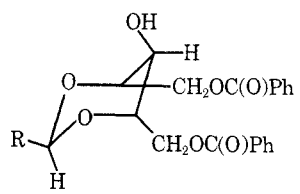
Received February 26, 1971

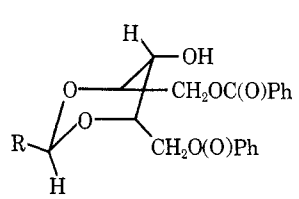
Second-order rate constants were determined for the esterification of 1,5-di-*O*-benzoyl-2,4-*O*-benzylidenexylitol (**1**) and -ribitol (**3**) and 1,5-di-*O*-benzoyl-2,4-*O*-methylenexylitol (**2**) and -ribitol (**4**) with acid anhydrides, carboxylic acid chlorides, and sulfonic acid chlorides in anhydrous pyridine. Acid anhydrides react more rapidly with compounds **3** and **4** with equatorial hydroxyl than compounds **1** and **2** with axial hydroxyl. The opposite order of reactivity was found for carboxylic acid chlorides and sulfonic acid chlorides. The Hammett correlation using σ^+ substituent constants was found to apply for reactions utilizing para-substituted benzoyl chlorides and benzenesulfonyl chlorides. Polar interactions are proposed to rationalize differences in reactivity.

Considerable attention has been directed toward comparisons of reactivities of secondary hydroxyl groups in carbohydrate derivatives in esterification and oxidation reactions.[1] Essentially all of the studies are based upon yield data and are directed toward synthetic goals rather than toward rationalization of the differences observed. Only a few esterification rate studies of alcohols with acid anhydrides or chlorides in anhydrous pyridine are reported in the literature.[2]

Four alcohols, 1,5-di-*O*-benzoyl-2,4-*O*-benzylidenexylitol (**1**) and -ribitol (**3**) and 1,5-di-*O*-benzoyl-2,4-*O*-methylenexylitol (**2**) and -ribitol (**4**), were selected as substrates for kinetic studies. These two pairs of stereoisomers had previously been found to exhibit markedly different reactivities. Hudson and coworkers[3]



1, R = Ph
2, R = H



3, R = Ph
4, R = H

reported that compound **1** was the sole isolable product in several attempts to prepare 1,3,5-tri-*O*-benzoyl-2,4-*O*-benzylidenexylitol from 2,4-*O*-benzylidenexylitol in pyridine with excess benzoyl chloride, whereas 2,4-*O*-methylenexylitol, 2,4-*O*-benzylideneribitol, and 2,4-*O*-methyleneribitol readily yield tribenzoates. Sera[4] reported that compounds **2**, **3**, and **4** are oxidized to the corresponding 3-ketoses with chromium trioxide–glacial acetic acid, but compound **1** is inert.

Amounts of compounds **1**, **2**, **3**, and **4** conveniently available for kinetic studies suggested the need for a method utilizing modest quantities. Details of the procedures developed are given in the Experimental Section. Previous studies[5] have shown that the second-order plots for reaction of alcohols and acid chlorides in pyridine are not linear. Correction for loss of acylating agent, as a consequence of hydrolysis by moisture present in pyridine, provided clean second-order plots.

Second-order rate constants are given in Table I for the esterification of compounds **1**–**4** with carboxylic acid anhydrides and acid chlorides and sulfonic acid chlorides. In comparing data obtained for reactions with acid anhydrides, several relationships emerge. The ribitol compounds (**3** and **4**) with an equatorial hydroxyl group are more reactive than the xylitol compounds (**1** and **2**), which have an axial hydroxyl group. This difference is expected on conformational grounds[6] and is the same order observed for the esterification of *cis*- and *trans*-4-phenylcyclohexanols[2a] and for *cis*- and *trans*-5-hydroxy-2-phenyl-1,3-dioxanes[2d] with aliphatic acid anhydrides in pyridine. The reactivity of all four substrates is substantially depressed as the number of methyl substituents on the α carbon of the anhydrides is increased. All four compounds failed to react with pivalic anhydride to an observable extent. The starting alcohols were recovered after being heated at 95° for 7 days with a 6–7-fold excess of pivalic anhydride in pyridine. The ratio of $k_{(MeCO)_2O}/k_{(EtCO)_2O}$ or $k_{(MeCO)_2O}/k_{(i\text{-}PrCO)_2O}$ is much larger for compounds **1**–**4** than for cyclohexanol and some of its derivatives. Data are given in Table II. Since the electronic effects of methyl substituents on the α carbon of the anhydrides should be similar in both series, the retarding effect observed with compounds **1**–**4** would appear to be largely steric in nature, the effect being more pronounced in the xylitol compounds **1** and **2**, in which the hydroxyl group is in the axial position.

It was somewhat surprising to observe that the rates of esterification of **1** and **3** with acetic anhydride in pyridine are greater than those of *cis*- and *trans*-5-hydroxy-2-phenyl-1,3-dioxanes (6×10^{-5} and 5×10^{-4} l. mol^{-1} sec^{-1}, respectively, at 25°), reported by Buck and coworkers.[2d] The presence of the bulky groups, benzoyloxymethyl, on the carbon atoms adjacent to the hydroxyl group in **1** and **3**, as contrasted to hydrogens in the other pair, might be expected to provide an inhibiting effect. Rate enhancement may be a consequence of suppression to change in ring conformation by the bulky substituents.

The greater reactivity of acid chlorides over acid anhydrides is to be expected. The greater reactivity of compounds **1** and **3**, containing the benzylidene acetal

(1) J. M. Sugihara, *Advan. Carbohyd. Chem.*, **8**, 1 (1953); R. S. Tipson, *ibid.*, **8**, 107 (1953); J. M. Sugihara and G. U. Yuen, *J. Amer. Chem. Soc.*, **79**, 5780 (1957); J. J. Willard, J. S. Brimacombe, and R. P. Brueton, *Can. J. Chem.*, **42**, 2560 (1964); J. M. Williams and A. C. Richardson, *Tetrahedron*, **23**, 1369 (1967).

(2) (a) E. L. Eliel and C. A. Lukach, *J. Amer. Chem. Soc.*, **79**, 5986 (1957); (b) R. L. Stutz, *Dissertation Abstr.*, **22**, 4192 (1962); (c) K. W. Buck, A. B. Foster, A. R. Perry, and J. M. Webber, *J. Chem. Soc.*, 4171 (1963); (d) K. W. Buck, J. M. Duxbury, A. B. Foster, A. R. Perry, and J. M. Webber, *Carbohyd. Res.*, **2**, 122 (1966).

(3) R. M. Hann, A. T. Ness, and C. S. Hudson, *J. Amer. Chem. Soc.*, **68**, 1769 (1946).

(4) A. Sera, *Bull. Soc. Chem. Jap.*, **35**, 2033 (1962).

(5) S. Yamada and S. Hayashi, *Tokai Denkyoku Giho*, **19** (1), 37 (1958); P. Mesnard, B. Gibirila, and M. Bertrucat, *C. R. Acad. Sci.*, **257**, (20), 2999 (1963); W. F. Edgell and L. Parts, *J. Amer. Chem. Soc.*, **77**, 4899 (1955).

(6) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, N. Y., 1962, p 204.

TABLE I

SECOND-ORDER ESTERIFICATION RATES IN PYRIDINE

Acylating agent[b]	Registry no.	T, °C	k_2[a] × 10^3 l. mol^{-1} sec^{-1}			
			1	2	3	4
$(MeCO)_2O$	108-24-7	25	0.335	0.146	1.62	1.26
$(MeCO)_2O$		35	0.571		2.36	
$(MeCO)_2O$		42.6	0.766		3.55	
$(MeCO)_2O$		50	1.11	0.501	4.81	3.48
$(EtCO)_2O$	123-62-6	50	0.243	0.101	1.35	1.15
$(i\text{-}PrCO)_2O$	97-72-3	50	0.0409	0.0187	0.299	0.223
i-PrCOCl	79-30-1	25	183		22.1	
PhCOCl	98-88-4	25	16.6	13.6	2.46	1.94
$p\text{-}CH_3OC_6H_4COCl$	100-07-2	25	3.18		0.547	
$p\text{-}CH_3C_6H_4COCl$	874-60-2	25	8.74		1.32	
$p\text{-}FC_6H_4COCl$	403-43-0	25	14.4		2.09	
$p\text{-}ClC_6H_4COCl$	122-01-0	25	22.2		3.07	
$p\text{-}BrC_6H_4COCl$	586-75-4	25	25.3		3.18	
$p\text{-}O_2NC_6H_4COCl$	122-04-3	25	162		15.7	
$MeSO_2Cl$	124-63-0	25	38.8	37.1	9.08	7.81
$MeSO_2Cl$		30			12.7	
$MeSO_2Cl$		35			16.5	
$EtSO_2Cl$	594-44-5	25	6.08	4.55	3.38	2.63
$PrSO_2Cl$	10147-36-1	25	3.16	3.00	2.54	2.41
$BuSO_2Cl$	2386-60-9	25	3.25	3.17	2.45	2.82
$PhSO_2Cl$	98-09-9	25	1.56	1.51		
$p\text{-}CH_3C_6H_4SO_2Cl$	98-59-9	25	0.75	0.90		
$p\text{-}CH_3C_6H_4SO_2Cl$		35	0.80			
$p\text{-}CH_3C_6H_4SO_2Cl$		45	1.45			
$p\text{-}CH_3OC_6H_4SO_2Cl$	98-68-0	25	0.39			
$p\text{-}FC_6H_4SO_2Cl$	349-88-2	25	1.42			
$p\text{-}ClC_6H_4SO_2Cl$	98-60-2	25	2.12			
$p\text{-}BrC_6H_4SO_2Cl$	98-58-8	25	2.53			
$p\text{-}O_2NC_6H_4SO_2Cl$	98-74-8	25	7.03			

[a] Rate constants reported are, with but few exceptions, averages of two or three duplicate runs. Deviation from the average was about ±2.5%; in many instances much less. Standard deviations of data points in establishing the best straight line within a given run were in some cases ±3% but generally much less. [b] Rates of reaction of **1** and **3** with benzoic anhydride were found to be slow and precluded determination of rate constants. However, **3** was more reactive than **1**. The same observation was made with pivaloyl chloride but the order of reactivity was **1** over **3**.

TABLE II

RATIO OF ESTERIFICATION RATE CONSTANTS

Substrate	$k_{(MeCO)_2O}/k_{(EtCO)_2O}$	$k_{(MeCO)_2O}/k_{(i\text{-}PrCO)_2O}$
1	4.6	27.1
2	5.0	26.8
3	3.6	16.1
4	3.0	15.6
Cyclohexanol[a]	1.5	1.9
cis-4-*tert*-Butylcyclohexanol[a]	1.3	1.3
trans-4-*tert*-Butylcyclohexanol[a]	1.5	2.0
trans-4-*tert*-Phenylcyclohexanol[a]		1.9

[a] Rate constants given in ref 2a.

ring, is consistent with the data obtained in esterification with acid anhydrides. The differences are smaller as would be expected because of the greater reactivity and lesser selectivity of acid chlorides. These observations suggest that the hydroxyl groups are located in much the same environment in each of the two series. Moreover, conformational changes occurring in the 1,3-dioxane rings during the course of the reactions must be limited. The difference in electronic or steric effects of phenyl *vs.* hydrogen would be expected to be small because of the distances from the reaction center. Though methanesulfonyl chloride exhibited greater reactivity toward all four alcohols than ethanesulfonyl chloride, 1-propanesulfonyl chloride, and 1-butanesulfonyl chloride, differences among the latter three were small.

The greater reactivity of acid chlorides toward the xylitol compounds with axial hydroxyl (**1** and **2**) over the ribitol compounds with equatorial hydroxyl (**3** and **4**) was unexpected, since the opposite order was observed for the carboxylic acid anhydrides. Though rate constants were not obtained using benzoic anhydride because of its relative inertness, preference of **3** and **1** was clearly established. Accordingly, relative reactivities in this sense are the same whether an aliphatic or aromatic anhydride is used as the acylating agent. However, this type of reversal in reactivities of anhydrides and acid chlorides is not without precedent in the literature.[2d] Reaction of acetic anhydride in pyridine with equimolar amounts of *cis*- (axial hydroxyl) and *trans*-5-hydroxy-2-phenyl-1,3-dioxane (equatorial hydroxyl) gave products in which the ratio of cis ester to trans ester was 1:5.8. The parallel reaction using *p*-phenylazobenzoyl chloride in pyridine provided a cis to trans product ratio of 5.6:1. A similar study with *cis*- and *trans*-4-phenylcyclohexanol demonstrated that the cis isomer (equatorial hydroxyl) was the more reactive toward both acetic anhydride and *p*-phenylazobenzoyl chloride. These and our observations suggest that the 1,3-dioxane ring has an important function in controlling reactivity. A similar comparison in the aromatic sulfonyl chloride series was not conveniently feasible since reactivities of substrates **3** and **4** were reduced to a point that kinetic measurements near ambient temperatures were precluded.

Rate constants (Table I) for reactions of para-substituted benzoyl chlorides and compounds **1** and **3** as well as para-substituted benzenesulfonyl chlorides and **1** were processed to establish Hammett correlations. Plots using σ values[7] were found to be nonlinear. Plots of log k *vs.* σ^+[8] are shown in Figure 1. Positive ρ values clearly evolve from the plots. Generally reactions giving $\rho\sigma^+$ relationships exhibit negative ρ values, for example, cumyl chloride solvolysis[8] and pyrolysis of 1-arylethyl acetates.[9] Two contrary examples[10] lending support to observations made in this study show positive ρ values in $\rho\sigma^+$ plots. In both instances, explanations are provided suggesting that the high contribution of conjugation of the substituent with the reaction site decreases in going from substrate to the activated complex in the rate-limiting process. Our data allow for a similar interpretation on the basis that substituted benzoyl chlorides interact with pyridine to form aroylpyridinium chlorides with considerable carbonium ion character.

An interpretation[2d] for the greater reactivity of *trans*-5-hydroxy-2-phenyl-1,3-dioxane toward acetic anhydride in pyridine and the cis isomer toward *p*-phenylazobenzoyl chloride in pyridine was given, based upon intramolecular hydrogen bonding. The same interpretation[2d] was provided for the observation[11] that 1,4:3,6-dianhydro-D-glucitol yields more of the 2(exo) acetate than 5(endo) acetate with acetic anhydride in pyridine but more of the 5 product when reacted with *p*-phenylazobenzoyl chloride or *p*-toluenesulfonyl chloride in pyridine. It would seem unlikely that intramolecular hydrogen bonding would persist to any extent in a pyridine solution of these compounds. Intermolecular hydrogen bonding between pyridine and alcohols is evident even in dilute solutions.[12]

Dipolar interactions greatly influence conformation of heterocyclic compounds.[13] We propose that dipolar interactions, both dipole–dipole and ion–dipole, serve as a more logical source of control of reactivity rather than hydrogen bonding effects. Acid anhydrides and acid chlorides react with pyridine to form intermediate acylpyridinium ions. The extent of conversion of acid chlorides to an acylpyridinium may be nearly quantitative.[14] On the other hand, acid anhydrides and pyridine do not yield isolable salts. The equilibration of acetic anhydride and pyridine with acetylpyridinium acetate was recently reported.[15] Thus the reactive species in acylation with an acid chloride in pyridine may be considered to be an acylpyridinium ion (**5** or **6**) while that with an acid anhydride is an ion pair (**7**). Though compounds with equatorial hydroxyl are more reactive toward acylation,[6] we suggest that the electronegative atoms in the 1,3-dioxane ring promote reactivity in the series with axial hydroxyl by interaction with the positive pyridine nitrogen. This type of interaction is precluded with the ribitol series in which hydroxyl is disposed in the equatorial position. The lack of definitive cationic character for species **7** formed from acid anhydrides and pyridine allows the normal order[6] of reactivity to prevail. The observation of positive ρ values in the Hammett $\rho\sigma^+$ correlations accords with the formation of a transition state in which the high contribution of conjugation of the substituent with the reaction site decreases. The contribution of para substituents in R_2 for structure **8** might be expected to be less than that of the same substituents in R of **5** or **6**.

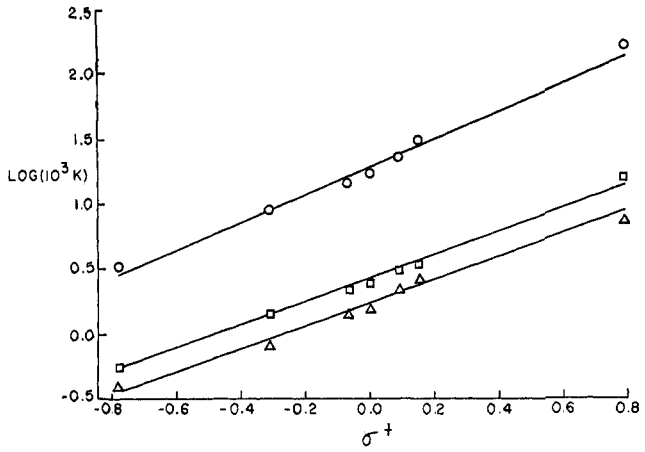
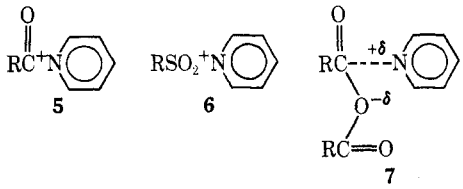
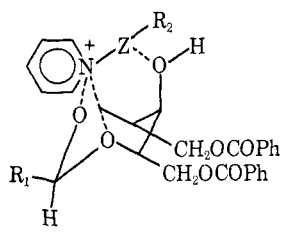


Figure 1.—Correlation of log k_2 with ρ^+. ○, **1** and para-substituted benzoyl chlorides, ρ = 0.95; linear correlation coefficient = 0.983. □, **3** and para-substituted benzoyl chlorides, ρ = 0.83; linear correlation coefficient = 0.987. △, **1** and para-substituted benzenesulfonyl chlorides, ρ = 0.85; linear correlation coefficient = 0.985.





8, Z = CO or SO_2

It is of interest to note that the contrasting reactivity of the *exo*- and *endo*-hydroxyl groups in 1,4:3,6-dianhydro-D-glucitol toward acetic anhydride and acid chlorides may be rationalized by this same interpretation. Numerous other examples may be cited and similarly interpreted; for example, the C_3-hydroxyl is more reactive than that on C_2 in methyl 4,6-*O*-benzylidene-α-D-galactopyranoside toward benzoyl chloride in pyridine, but the C_2-hydroxyl is the more reactive secondary hydroxyl in methyl 4,6-*O*-benzylidene-α-D-glycopyranoside.[16] Similarly, a variety of examples of relative reactivities of hydroxyl groups in sulfonation may be

(7) L. P. Hammett, "Physical Organic Chemistry," 2nd ed, McGraw-Hill, New York, N. Y., 1970, p 356.
(8) H. C. Brown and Y. Okamoto, *J. Amer. Chem. Soc.*, **80**, 4979 (1958).
(9) R. Taylor, G. G. Smith, and W. H. Wetzel, *ibid.*, **84**, 4817 (1962).
(10) K. K. Lum and G. G. Smith, *J. Org. Chem.*, **34**, 2095 (1969); R. J. Sundberg and C. C. Lang, *ibid.*, **36**, 300 (1971).
(11) (a) R. U. Lemieux and A. G. McInnes, *Can. J. Chem.*, **38**, 136 (1960); (b) K. W. Buck, A. B. Foster, A. R. Perry, and J. M. Webber, *J. Chem. Soc.*, 4171 (1963).
(12) T. J. V. Findlay and A. D. Kidman, *Aust. J. Chem.*, **18**, 521 (1965).
(13) E. L. Eliel and C. A. Giza, *J. Org. Chem.*, **33**, 3754 (1968); E. L. Eliel and S. H. Schroeter, *J. Amer. Chem. Soc.*, **87**, 5031 (1965); R. O. Hutchins, L. D. Kopp, and E. L. Eliel, *ibid.*, **90**, 7174 (1968); E. L. Eliel, *Kem. Tidskr.*, **81**, No. 6/7, 22 (1969).
(14) H. E. Baumgarten, *J. Amer. Chem. Soc.*, **75**, 1239 (1953).
(15) A. R. Fersht and W. P. Jencks, *ibid.*, **91**, 2125 (1969).
(16) R. W. Jeanloz and D. A. Jeanloz, *ibid.*, **79**, 2579 (1957).

rationalized by this interpretation. Some are the greater reactivity of the 5-hydroxyl over the 2-hydroxyl in 1,4:3,6-dianhydro-D-glucitol toward *p*-toluenesulfonyl chloride;[11a] the greater reactivity of 1,4:3,6-dianhydro-D-glucitol 2-*p*-toluenesulfonate over 1,4:3,6-dianhydro-D-glucitol 5-*p*-toluenesulfonate toward *p*-toluenesulfonyl chloride;[11b] and preference for 3-O-tosylation in methyl 4,6-*O*-benzylidene-α- (or -β-) D-galactopyranoside.[17] Numerous other examples described[18] may be similarly rationalized.

Rate measurements at several temperatures were determined for a few of the reactions studies. Data are given in Table I. Activation parameters calculated are listed in Table III. This limited study of temperature dependence precludes generalization.

TABLE III

ACTIVATION PARAMETERS[a]

Reactions	$\Delta H^{\pm}$, kcal/mol	$\Delta S_{25}^{\pm}$, eu
1 + $(MeCO)_2O$	8.4 ± 0.3	−46 ± 4
2 + $(MeCO)_2O$	8.8	−47
3 + $(MeCO)_2O$	7.7 ± 0.2	−45 ± 4
4 + $(MeCO)_2O$	7.1	−48
1 + p-$CH_3C_6H_4SO_2Cl$	11.0 ± 0.7	−51 ± 4
3 + CH_3SO_2Cl	12.2 ± 0.4	−26 ± 9

[a] Standard deviations given.

Experimental Section[19]

Pyridine was refluxed over BaO for 16–24 hr and then fractionally distilled through a packed column. The fraction boiling at 114–114.5° was collected in a moisture-protected receiver and stored over KOH pellets in an automatic buret. Aniline, used for determining per cent anhydride, was distilled prior to use, collecting that fraction boiling at 88° (21–22 mm). All acylating agents were purified by distillation and/or recrystallization: acetic anhydride, bp 139° (745 mm); propionic anhydride, bp 68–69° (20 mm); isobutyric anhydride, bp 75–76° (20 mm); pivalic anhydride, bp 98–99° (31 mm); isobutyryl chloride, bp 91°; benzoyl chloride, bp 93° (21 mm); *p*-chlorobenzoyl chloride, 108–109° (12 mm); *p*-fluorobenzoyl chloride, bp 81° (12 mm); *p*-anisoyl chloride, bp 141° (12 mm); *p*-toluoyl chloride, bp 102° (15 mm); *p*-bromobenzoyl chloride, mp 38–39° (recrystallized from dry, low-boiling ligroin); *p*-nitrobenzoyl chloride, mp 71–72° (recrystallized from dry, low-boiling ligroin); methanesulfonyl chloride, bp 57–58° (12 mm); ethanesulfonyl chloride, bp 73° (18 mm); 1-propanesulfonyl chloride, bp 81–85° (15 mm); 1-butanesulfonyl chloride, bp 98–101° (18 mm); benzenesulfonyl chloride, bp 92° (16 mm); *p*-toluenesulfonyl chloride, bp 87–88° (14 mm); *p*-chlorobenzenesulfonyl chloride, bp 97–100° (15 mm), mp 50° (recrystallized from chloroform–ligroine); *p*-bromobenzenesulfonyl chloride, bp 141–142° (5 mm), mp 68° (recrystallized from ligroin); *p*-fluorobenzenesulfonyl chloride, mp 32° (recrystallized from ligroin); *p*-nitrobenzenesulfonyl chloride, mp 80° (recrystallized from ligroin); and *p*-methoxybenzenesulfonyl chloride, mp 42° (recrystallized from chloroform–ligroin).

1,5-Di-*O*-benzoyl-2,4-*O*-benzylidenexylitol (1) was prepared by the method of Hann, Ness, and Hudson[3] with some modifications. The filtrate containing the cleavage product from the reaction of 2,4-*O*-benzylidene-D-glucitol and sodium metaperiodate was cooled and $NaBH_4$ (20% excess) was slowly added. After 30 hr at room temperature, the pH of the reaction mixture was adjusted to approximately 5 by addition of 3 *M* acetic acid and filtered, and resulting solution was concentrated on an air stream. The recrystallized product melted at 149.5–150° (reported[3] mp 148–149°).

1,5-Di-*O*-benzoyl-2,4-*O*-methylenexylitol (2) was prepared by modification of the method of Hann, Ness, and Hudson.[20] $NaBH_4$ (20% excess) was slowly added to the ice–water-cooled filtrate containing the cleavage product from the reaction of 2,4-*O*-methylene-D-glucitol (10.0 g) and sodium metaperiodate. The solution was allowed to stand at room temperature for 30 hr and then an ion exchanger (H^+ form) was added to the reaction mixture and after 30 min the solution was filtered and the filtrate air-evaporated. The resulting residue was dissolved in 100 ml of CH_3OH and vacuum evaporated. This was repeated twice. Extraction of the residue for 48 hr by means of a Soxhlet extractor using 300 ml of $CHCl_3$ provided impure 2,4-*O*-methylenexylitol upon evaporation of solvent. Following two recrystallizations from absolute EtOH, benzoylation was effected using 2.2 mol of acylating agent per mol of the 2,4-*O*-methylenexylitol to provide product, mp 140–141° (reported[20] mp 139–140°).

1,5-Di-*O*-benzoyl-2,4,*O*-benzylideneribitol, mp 136.5–138°, was prepared by the method previously reported.[21]

1,5-Di-*O*-benzoyl-2,4,*O*-methyleneribitol, mp 164–166°, was prepared by the method previously reported.[22]

3-*O*-Acyl Derivatives of Compounds 1–4.—To a cold solution of 0.2–0.3 g of alcohol in 10 ml of anhydrous pyridine, 2–3-mol excess of the acylating or sulfonating agent was added dropwise. After the solution was allowed to stand at room temperature for 24–48 hr, a few drops of H_2O was added, and then the mixture was poured into 300–400 ml of 10–15% aqueous $NaHCO_3$. The aqueous solution was extracted with $CHCl_3$ and the extract washed successively with 1 *N* HCl, 5% aqueous $NaHCO_3$, and H_2O. The chloroform solution was dried over anhydrous $CaCl_2$, filtered, and evaporated to dryness. The crude products, obtained in essentially quantitative yield, were recrystallized 4–5 times from EtOH and dried *in vacuo*. Analytical data are given in Table IV.

Kinetic Method.—The typical method[2a] of following esterification kinetics by volumetric titration was modified by utilizing an automatic titration procedure requiring less than 0.2 g of alcohol, 1–4, per kinetic run. The automatic titrator consisted of a Radiometer TTT 11 control unit and a titration assembly designed by Stewart[23] with a sensitivity of 5×10^{-5} ml.

Preliminary experiments demonstrated that excess anhydride in pyridine is almost instantaneously hydrolyzed upon addition of small amounts of H_2O to yield 2 mol of acid in the quenching process. Hydrolysis of ester under conditions imposed was not detectable. Thus the decrease in acid titer as the reaction proceeds is directly related to the amount of ester formed or to the amount of alcohol and anhydride consumed.

In a typical kinetic run, the alcohol (about 4×10^{-4} mol), 1–4, was accurately weighed into a 10-ml volumetric flask and dissolved by partially filling the flask with anhydrous pyridine. A 10-ml stock solution of the anhydride in pyridine was prepared so that the number of moles of anhydride[24] in a 1-ml aliquot of the stock solution equaled the number of moles of alcohol weighed out. Then 1 ml of the stock solution was added to the alcohol solution and anhydrous pyridine added to provide 10 ml of reaction mixture. The flask was sealed with a serum cap and placed in a constant temperature bath (±0.1°). Aliquots of 1 ml were withdrawn periodically with a syringe, previously purged with dry N_2 to minimize introduction of moisture into the reaction mixture. Each aliquot was quenched by introduction into a 100-ml beaker containing a few drops of H_2O, and the resulting solution was stirred for 1–2 min. An additional 10 ml of H_2O was added and the mixture stirred until the alcohol and ester precipitated or oiled out. CCl_4 (10 ml) was added to the beaker to dissolve the alcohol and ester and to depress the extent of hydrolysis of the ester during the titration. Another 30 ml of H_2O was added and the resulting mixture was titrated to a pH of 8.7 with standard NaOH, contained in the 1-ml titrator syringe.

The kinetic method was modified in one respect for acid chlorides. An infinite-time titrimetric method[2b] was employed in order to make a correction for water contained in the pyridine. Although good linear plots up to 60–75% conversion were ob-

(17) M. Gyr and T. Reichstein, *Helv. Chim. Acta*, **28**, 226 (1945); A. C. Mackly and T. Reichstein, *ibid.*, **30**, 496 (1947); H. Huber and T. Reichstein, *ibid.*, **31**, 1645 (1948).

(18) D. H. Ball and F. W. Parris, *Advan. Carbohyd. Chem.*, **23**, 233 (1968).

(19) Melting points were determined on a Fisher-Johns apparatus and are not corrected. Elemental analyses were performed by the Australian Microanalytical Service.

(20) R. M. Hann, A. T. Ness, and C. S. Hudson, *J. Amer. Chem. Soc.*, **66**, 670 (1944).

(21) S. M. Dorrence, Ph.D. Dissertation, University of Utah, 1964.

(22) R. M. Hann and C. S. Hudson, *J. Amer. Chem. Soc.*, **66**, 1906 (1944).

(23) We thank Dr. J. Stewart, University of North Dakota, Grand Forks, for allowing us to fabricate a unit, following his design.

(24) Acid anhydrides were periodically assayed by the method described by E. L. Eliel and F. J. Biros, *J. Amer. Chem. Soc.*, **88**, 3334 (1966).

TABLE IV

3-O-ACYL AND SULFONYL DERIVATIVES OF COMPOUNDS 1–4

Compd[a]	Mp, °C	Compd[a]	Mp, °C
3-*O*-Acetyl-**1**	128.5–129[b]	**1** 3-benzenesulfonate	153–154
3-*O*-Propionyl-**1**	99–100	**1** 3-*p*-toluenesulfonate	156–157
3-*O*-Isobutyryl-**1**	96.5–97.5	**1** 3-*p*-nitrobenzenesulfonate	158–159
3-*O*-Acetyl-**2**	176.5–177[c]	**1** 3-*p*-bromobenzenesulfonate	161–163
3-*O*-Propionyl-**2**	104–105	**1** 3-*p*-chlorobenzenesulfonate	160–162
3-*O*-Isobutyryl-**2**	79–80	**1** 3-*p*-fluorobenzenesulfonate	167–168
3-*O*-Acetyl-**3**	108–109[d]	**1** 3-*p*-methoxybenzenesulfonate	162–163
3-*O*-Propionyl-**3**	121–122	**1** 3-methanesulfonate	178–179
3-*O*-Isobutyryl-**3**	101.5–102	**1** 3-ethanesulfonate	180–182
3-*O*-Acetyl-**4**	101.5–102.5	**1** 3-(1-propanesulfonate)	181–182
3-*O*-Propionyl-**4**	100–100.5	**1** 3-(1-butanesulfonate)	182–184
3-*O*-Isobutyryl-**4**	55–57	**2** 3-benzenesulfonate	143–144
3-*O*-Benzoyl-**1**	128–129	**2** 3-*p*-toluenesulfonate	146–147
3-*O*-*p*-Bromobenzoyl-**1**	120–121	**2** 3-methanesulfonate	166–168
3-*O*-*p*-Chlorobenzoyl-**1**	108–109	**2** 3-ethanesulfonate	167–169
3-*O*-*p*-Fluorobenzoyl-**1**	103–104.5	**2** 3-(1-propanesulfonate)	168–169
3-*O*-*p*-Anisoyl-**1**	97–98.5	**2** 3-(1-butanesulfonate)	169–170
		3 3-methanesulfonate	135–137
3-*O*-*p*-Toluoyl-**1**	116–117	**3** 3-ethanesulfonate	136–138
3-*O*-*p*-Nitrobenzoyl-**1**	142.5–144	**3** 3-(1-propanesulfonate)	137–138
3-*O*-Benzoyl-**2**	118–119[e]	**3** 3-(1-butanesulfonate)	138–140
3-*O*-Benzoyl-**3**	129–130[f]	**4** 3-methanesulfonate	180–182
3-*O*-*p*-Bromobenzoyl-**3**	158–159	**4** 3-ethanesulfonate	182–183
3-*O*-*p*-Chlorobenzoyl-**3**	147–148	**4** 3-(1-propanesulfonate)	183–184
3-*O*-*p*-Fluorobenzoyl-**3**	135.5–136.5	**4** 3-(1-butanesulfonate)	184–186
3-*O*-*p*-Anisoyl-**3**	106–107		
3-*O*-*p*-Toluoyl-**3**	101–102		
3-*O*-*p*-nitrobenzoyl-**3**	138–139		
3-*O*-*p*-Benzoyl-**4**	110.5–111[g]		

[a] Satisfactory combustion analytical data (±0.4%) were provided for all new compounds: Ed. [b] Reported mp 128–129°: G. Y. Wu and J. M. Sugihara, *Carbohyd. Res.*, **13**, 89 (1970). [c] Reported mp 174.5–175°, ref 4. [d] Reported mp 108–109°, reference in *b*. [e] Reported mp 117–118°, ref 20. [f] Reported mp 108–109, ref 21. [g] Reported mp 109–110°, ref 22.

tained for the acid anhydrides, curvature early in the kinetic run was observed for reactions with acid chlorides. The curvature is attributable to traces of water in the pyridine. Since the rate of hydrolysis of acid chlorides is considerably greater than the rate of esterification, the actual concentration of acid chloride was considered to be equal to the initial concentration minus the amount hydrolyzed.

Slopes for second-order rate plots were determined by the method of least squares[25] and processed on a computer. Activation parameters were calculated by applying the absolute rate equation.[26] For kinetic runs carried out at temperatures above 25°, corrections were made to account for thermal expansion of pyridine.

Registry No.—**1**, 31568-92-0; 3-*O*-propionyl-**1**, 31568-93-1; 3-*O*-isobutyryl-**1**, 31568-94-2; 3-*O*-benzoyl-**1**, 31568-95-3; 3-*O*-*p*-bromobenzoyl-**1**, 31568-96-4; 3-*O*-*p*-chlorobenzoyl-**1**, 31615-31-3; 3-*O*-*p*-fluorobenzoyl-**1**, 31568-97-5; 3-*O*-*p*-anisoyl-**1**, 31568-98-6; 3-*O*-*p*-toluoyl-**1**, 31568-99-7; 3-*O*-*p*-nitrobenzoyl-**1**, 31569-00-3; **1** 3-benzenesulfonate, 31569-01-4; **1** 3-*p*-toluenesulfonate, 31569-02-5; **1** 3-*p*-nitrobenzenesulfonate, 31569-03-6; **1** 3-*p*-bromobenzenesulfonate, 31569-04-7; **1** 3-*p*-chlorobenzenesulfonate, 31569-05-8; **1** 3-*p*-fluorobenzenesulfonate, 31569-06-9; **1** 3-*p*-methoxybenzenesulfonate, 31569-07-0; **1** 3-methanesulfonate, 31569-08-1; **1** 3-ethanesulfonate, 31569-09-2; **1** 3-(1-propanesulfonate), 31569-10-5; **1** 3-(1-butanesulfonate), 31569-11-6; **2**, 31569-12-7; 3-*O*-propionyl-**2**, 31569-13-8; 3-*O*-isobutyryl-**2**, 31569-14-9; **2** 3-benzenesulfonate, 31569-15-0; **2** 3-*p*-toluenesulfonate, 31569-16-1; **2** 3-methanesulfonate, 31569-17-2; **2** 3-ethanesulfonate, 31569-18-3; **2** 3-(1-propanesulfonate), 31569-19-4; **2** 3-(1-butanesulfonate), 31569-20-7; **3**, 31569-21-8; 3-*O*-propionyl-**3**, 31569-22-9; 3-*O*-isobutyryl-**3**, 31569-23-0; 3-*O*-*p*-bromobenzoyl-**3**, 31569-24-1; 3-*O*-*p*-chlorobenzoyl-**3**, 31569-25-2; 3-*O*-*p*-fluorobenzoyl-**3**, 31569-26-3; 3-*O*-*p*-anisoyl-**3**, 31569-27-4; 3-*O*-*p*-toluoyl-**3**, 31569-28-5; 3-*O*-*p*-nitrobenzoyl-**3**, 31569-29-6; **3** 3-methanesulfonate, 31569-30-9; **3** 3-ethanesulfonate, 31569-31-0; **3** 3-(1-propanesulfonate), 31638-55-8; **3** 3-(1-butanesulfonate), 31569-32-1; **4**, 31569-33-2; 3-*O*-acetyl-**4**, 31569-34-3; 3-*O*-propionyl-**4**, 31569-35-4; 3-*O*-isobutyryl-**4**, 31569-36-5; **4** 3-methanesulfonate, 31569-37-6; **4** 3-ethanesulfonate, 31569-38-7; **4** 3-(1-propanesulfonate), 31569-39-8; **4** 3-(1-butanesulfonate), 31572-15-3.

Acknowledgment.—The support by the National Science Foundation (GP-5736) is gratefully acknowledged.

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(26) S. Glasstone, K. J. Laidler, and H. Eyring, "The Theory of Rate Processes," McGraw-Hill, New York, N. Y., 1941, p 14.