Stereoselective and Stereospecific Reactions. III.[1] Benzoylation, Cyclization, and Epimerization of Diols

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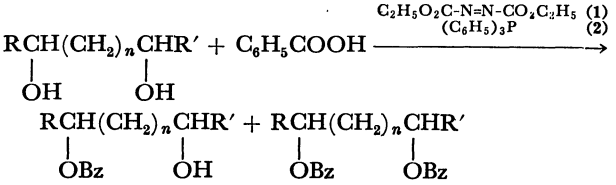
The benzoylation of various classes of diols by means of diethyl azodicarboxylate (**1**) and triphenylphosphine (**2**) was carried out at room temperature. When primary-secondary diols were treated with an equimolar amount of benzoic acid (**3**) in the presence of 1.5 molar equivalents of **1** and **2**, reaction mainly occurred at their primary hydroxyl functions. Secondary-secondary diols gave mono- and dibenzoylated products or cyclic ethers. The course of the reactions depends on the structure of diols used. Thus, intermolecular displacement giving benzoates is a favorable process for 1,3-butanediol, 2,4-pentanediol and *trans*-1,2-indanediol, while 2,5-hexanediol and *trans*-1,2-cyclohexanediol afford the cyclized products.

For the past several years studies have been carried out on the intermolecular dehydration between alcohols and active hydrogen compounds by means of diethyl azodicarboxylate (**1**) and triphenylphosphine (**2**). The reaction of nucleosides with dibenzyl hydrogen phosphate and with benzoic acid (**3**) in the presence of **1** and **2** predominantly gave 5′-*O*-phosphorylated and 5′-*O*-benzoylated products, respectively.[2] Stereospecificity and functional selectivity were also observed in the alkylation of imides.[3] Bose *et al.*[4] reported that the present system could be utilized in the inversion of unhindered sterol configuration. In this paper, we wish to report the benzoylation of simple diols by the use of **1** and **2**.

Primary, Secondary-Diols. When 1,3-butanediol was allowed to react with an equimolar amount of **3** in the presence of 1.5 molar equivalents of **1** and **2** at room temperature, 3-hydroxybutyl benzoate was formed in a 70% yield. A small amount (7%) of dibenzoylated product was also isolated. Similarly, 1-phenyl-1,2-ethanediol or 3-chloro-1,2-propanediol predominantly gave monobenzoate. When 1.5 molar equivalent of **3** was used in the benzoylation of 1,3-butanediol, the yields of 3-hydroxybuthyl benzoate and 1,3-bis(benzoyloxy)butane increased to 80% and 10%, respectively. The results are summarized in Table 1.



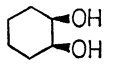
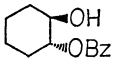
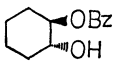
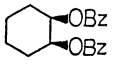
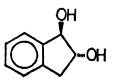
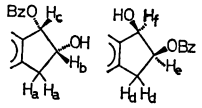
Scheme 1

Table 1. Benzoylation of primary-secondary diols and monobenzoates

Diol or monobenzoate	Product	Yield %	Tlc[a] I	Tlc[a] II	NMR chemical shift (δ) in CCl_4 at 60 MHz
$CH_3CHCH_2CH_2OH$ (OH)	$CH_3CHCH_2CH_2OBz$ (OH)	70		B-M (10 : 1)	CH_3(1.22 d), $\rangle C-CH_2-C\langle$ (1.82 q) $\rangle CH$(3.93 m), $-CH_2O-$(4.40 t)
	$CH_3CHCH_2CH_2OBz$ (OBz)	7	E-PE (1 : 1)		CH_3(1.45 d), $\rangle C-CH_2-C\langle$ (2.15 q) $-CH_2-O-$(4.43 t), $\rangle CH$(5.35 sextet)
$CH_3CHCH_2CH_2OBz$ (OH)	$CH_3CHCH_2CH_2OBz$ (OBz)	63	E	B-M (5 : 1)	
$ClCH_2CHCH_2OH$ (OH)	$ClCH_2CHCH_2OBz$ (OH)	47			Cl-CH_2-(3.6 two lines, AB_2), $\rangle CH$ (3.5—4.3 m), $-CH_2-O-$(4.35 two lines, AB_2)
	$ClCH_2CHCH_2OBz$ (OBz)	5	B-EA (10 : 1)		Cl-CH_2-(3.88 d), $-CH_2-O-$(4.66 d) $\rangle CH$(5.55 quintet)
$ClCH_2CHCH_2OBz$ (OH)	$ClCH_2CHCH_2OBz$ (OBz)	81	B-EA (5 : 1)	C	
$C_6H_5CHCH_2OH$ (OH)	$C_6H_5CHCH_2OBz$ (OH)	47			$\rangle CH_2$(3.75 d, broad), $\rangle CH$(5.95 t, broad)
	$C_6H_5CHCH_2OBz$ (OBz)	5	B-E (1 : 2)		$\rangle CH_2$(4.57 d), $\rangle CH$(6.30 t)

a) I=Solvent system used for separation. II=Solvent system used for purification. Solvents are benzene (B), ether (E), petroleum ether (PE), ethyl acetate (EA), methanol (M), and chloroform (C).

Table 2. Benzoylation of secondary-secondary diols and monobenzoates

Diol or monobenzoate	Product	Yield %	Tlc[a]	NMR chemical shift (δ) in CCl_4 at 60 MHz
$CH_3CH(OH)CH(OH)CH_3$	$CH_3CH(OH)CH(OBz)CH_3$	8	E-PA (1 : 1)	CH_3CHOH(1.17 d), CH_3CHOBz(1.30 d), >CHOH(3.8 quintet), >CHOBz(4.85 quintet)
$CH_3CH(OH)CH_2CH(OH)CH_3$	$CH_3CH(OH)CH_2CH(OBz)CH_3$	57	E-PA (1 : 1)	CH_3CHOH(1.25 d), CH_3CHOBz(1.38 d), >CHOH(3.73 sextet), >CHOBz(5.35 sextet)
	$CH_3CH(OBz)CH_2CH(OBz)CH_3$	20		CH_3(1.39 d), $>CH_2$(2.03 t), >CHO-(5.27 sextet)
$CH_3CH(CH_2)_2CH(OBz)CH_3$ (OH)	$CH_3CH(CH_2)_2CH(OBz)CH_3$	75	E-PA (1 : 5)	CH_3(1.33 d), $-(CH_2)_2-$(1.6—1.9 m), >CHO-(4.8—5.4 m)
		22	E-PA (2 : 3)	$-(CH_2)_4-$(1.0—2.3 m), >CHOH(3.7—4.1 m), >CHOBz(4.8—5.2 m)
		60	E-PA (1 : 1)	$-(CH_2)_4-$(1.2—2.5 m), >CHO-(5.15—5.5 m)
		50[b]	B	H_a(2.95 d), H_b(4.48 q), H_c(5.95 d) H_d(3.05 d), H_e(5.42 q), H_f(5.04 d)

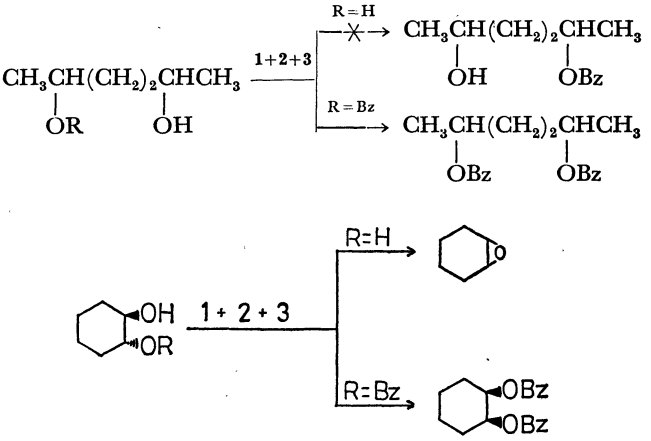
a) Solvent systems used for separation of products. See Table 1. b) The ratio of the 1-benzoylated and 2-benzoylated products is 1.4 : 1.

3-Hydroxybutyl benzoate and 3-chloro-2-hydroxypropyl benzoate reacted smoothly with **3** under the above conditions to give 1,3-bis(benzoyloxy)butane and 1,2-bis(benzoyloxy)-3-chloropropane in good yields.

Primary, Primary-Diols and Secondary, Secondary-Diols. Under the same conditions as for the reaction of primary–secondary diols, 1,3-propanediol gave 3-hydroxypropyl benzoate and 1,3-bis(benzoyloxy)propane in 65% and 12% yields, respectively. 1,4-Butanediol afforded monobenzoate and dibenzoate in 66% and 15% yields, respectively.

The benzoylation of secondary–secondary diols was then attempted. The reaction of 2,4-pentanediol with 1.5 molar equivalents of **1**, **2** and **3** proceeded with ease giving 4-hydroxy-2-pentyl benzoate and bis(benzoyloxy)pentane in 57% and 20% yields, respectively. *trans*-1,2-Indanediol gave a mixture of 1-hydroxy-2-benzoyloxy- and 1-benzoyloxy-2-hydroxyindanes in a 50% yield. 2,3-Butanediol, 2,5-hexanediol or *trans*-1,2-cyclohexanediol hardly gave benzoylated products. On the other hand, 5-benzoyloxy-2-hexanol and *trans*-2-benzoyloxycyclohexanol reacted smoothly with **3** in the presence of **1** and **2** to give 2,5-bis(benzoyloxy)hexane and 1,2-bis(benzoyloxy)cyclohexane in good yields. The results are summarized in Table 2.

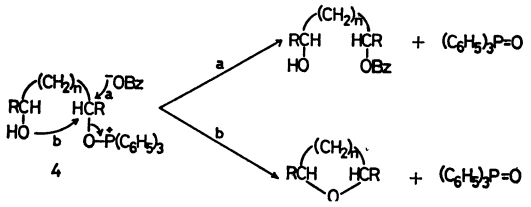
Secondary–secondary 1,2- and 1,4-diols gave no corresponding benzoates, while monobenzoates of these diols were converted into dibenzoates. The contrast between these reactions can therefore be explained by assuming the facile formation of three- and five-membered cyclic ethers. In order to confirm cyclization, the mixture resulting from the reaction of *trans*-1,2-cyclohexanediol with **1**, **2** and **3** was subjected to gas chromatography(glc). The resulting chromatogram revealed the formation of cyclohexene oxide in an 82% yield.



Scheme 2

The cyclization reaction would be rationalized in terms of intramolecular participation by a neighboring hydroxyl group in the initial alkoxyphosphonium salt (**4**) presumed as an intermediate of the present reaction.[5] If steric crowding renders intermolecular displacement slow and the hydroxyl group in the substrate molecule is at a suitable distance from the carbon site of substitution, three- or five- membered ring formation takes place predominantly. Somewhat related cases of cyclization have been observed in the reaction of

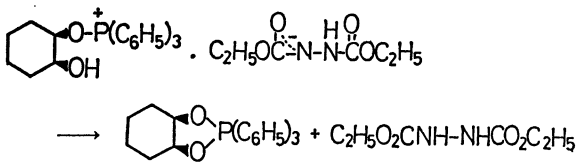
nucleosides.[6]



Scheme 3.

When 2,5-hexanediol was allowed to react with **1** and **2** in the absence of **3** at room temperature, 2,5-dimethyloxolane was formed in a 48% yield as determined by glc. The 2,5-dimethyloxolane was isolated by preparative glc and identified by comparison of its NMR spectrum with that of an authentic sample. Similarly, *trans*-1,2-cyclohexanediol and 1-phenyl-1,2-ethanediol were converted into the corresponding oxiranes.

Compared with the benzoylation of acyclic diols, *cis*-1,2-cyclohexanediol gave the benzoate in low yield (22%). The difference would be ascribed in part to conformational strain.[7] Although no direct evidence could be obtained, the formation of 1,2-*O*-(triphenyl)-phosphoranylcyclohexane (**5**) can not be ruled out.[8]



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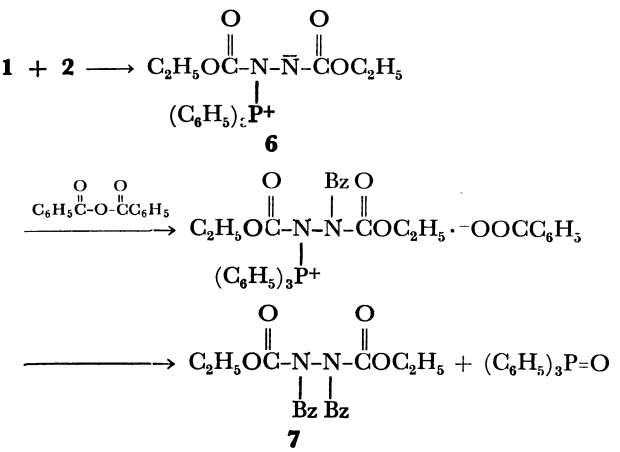
Scheme 4.

In some cases, for example in the benzoylation of *trans*-2-benzoyloxycyclohexanol, a small amount of *N,N'*-dibenzoyl-*N,N'*-bis(ethoxycarbonyl)hydrazine (**7**) was isolated. The formation of **7** would be explained as follows. Intermolecular dehydration between alcohols and carboxylic acids by means of **1** and **2** proceeds through initial activation of the alcohol.[5] In the reaction using sterically crowded alcohols, however, it is most likely that activation of carboxylic acid occurs to some extent giving the corresponding acid anhydride.[9] The anhydride fomed in turn reacts with the phosphonium salt (**6**) to afford **7**. In order to confirm this process, **1** was allowed to react with **2** in the presence of benzoic anhydride, **7** being isolated in an 80% yield.



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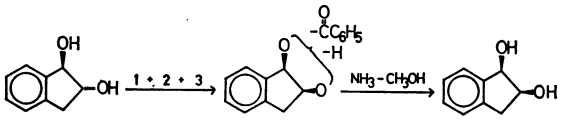
Scheme 5.

Stereochemistry. In order to examine the stereochemistry of the benzoylation of diols using a combination of **1** and **2**, a mixture of 1-hydroxy-2-benzoyloxy- and 1-benzoyloxy-2-hydroxyindanes, prepared from *trans*-1,2-indanediol, was treated with ammonia saturated in methanol affording *cis*-1,2-indanediol in a 60% yield. That 2-benzoyloxycyclohexanol derived from *cis*-1,2-cyclohexanediol by the present procedure has *trans*-configuration was proved by comparison of its NMR and IR spectra with those of an authentic sample.



Scheme 6.

Experimental

Nuclear magnetic resonance spectra were measured on a Hitachi R-20 spectrometer using tetramethylsilane as an internal standard. Mass spectra were obtained at 70 eV on a Hitachi 6M-GC gas-chromatogram-mass spectrometer, infrared spectra on a JASCO-IRG. Gas-chromatographic analyses were performed on a Hitachi 063 instrument with a flame ionization detector, and 1 m×3 mm column of 20% SE-30 on Celite 545 (60—80 mesh). Preparative separation of cyclic ethers was made on a Shimadzu GC-1C gas chromatograph with a 1.82 m×1 cm column of 20% SE-30 on Celite 545 (60—80 mesh). Thin layer separation was carried out on silica gel PF_{254} (Merck: 20 cm×20 cm or 20 cm×30 cm) and visualization was by UV light.

Diethyl azodicarboxylate,[10] 2,4-pentanediol,[11] 1-chloro-3-benzoyloxy-2-propanol,[12] *cis*- and *trans*-1,2-cyclohexanediols,[13,14] and *trans*-1,2-indanediol[15] were prepared by procedures in literature. *cis*-2-Benzoyloxycyclohexanol was prepared in a yield of 54% by the reaction of *cis*-1,2-cyclohexanediol (348 mg, 3 mmol) with benzoic anhydride (678 mg, 3 mmol) in pyridine for 12 hr. The product was isolated by preparative tlc (ether-petroleum ether 1 : 1). Similarly, *trans*-2-benzoyloxycyclohexanol was prepared in a 63% yield. 5-Benzoyloxy-2-hexanol was prepared in a 33% yield by the reaction of 2,5-hexanediol (354 mg, 3 mmol) with benzoic anhydride (678 mg, 3 mmol) in pyridine at room temperature for 4 hr, followed by tlc separation (ether-petroleum ether 1 : 5).

General Procedure of Benzoylation of Diols and their Monobenzoates. A solution of **1** (261 mg, 1.5 mmol) in tetrahydrofurane (THF, 2 ml) was added dropwise over a period of 1 hr to a solution of primary-primary diol or primary-secondary-diol (1 mmol), **2** (393 mg, 1.5 mmol) and **3** (122 mg, 1 mmol) in THF (2 ml) with stirring at room temperature. After 12—14 hr, the mixture was fractionated by preparative tlc.

In the case of benzoylation of secondary-secondary diols, 1.5 molar equivalent of **3** was used.

Benzoylation of trans-*1,2-Indanediol.* A solution of **1** (261 mg, 1.5 mmol) in 2 ml of THF was added dropwise to a solution of *trans*-1,2-indanediol (150 mg, 1 mmol), **2** (393 mg,

1.5 mmol) and **3** (183 mg, 1.5 mmol) in THF (3 ml) under reflux. After the solution had been refluxed for 5 hr, a mixture of 1-benzoyloxy-2-hydroxyindane and 1-hydroxy-2-benzoyloxyindane was isolated by tlc (benzene) in a 50% yield. The ratio was calculated to be 1.4 : 1 from the integration of NMR absorption. When the reaction was carried out at room temperature, the yield of the mixture of the monobenzoates decreased to 30%.

cis-*1,2-Indanediol.* The mixture of monobenzoates obtained by the reaction of *trans*-1,2-indanediol with **1, 2** and **3** was treated with methanol saturated with ammonia at room temperature for 24 hr. After removal of the solvent, *cis*-1,2-indanediol was isolated in a 60% yield by preparative tlc. The *cis*-diol was recrystallized from ethyl acetate–petroleum ether, mp 94—96 °C (lit.[15] mp 98 °C).

Cyclization of Diols. Cyclohexene Oxide. A solution of **1** (1.74 g, 10 mmol) in ether (8 ml) was added dropwise over a period of 2 hr at room temperature to a solution of *trans*-1,2-cyclohexanediol (1.16 g, 10 mmol) and **2** (2.62 g, 10 mmol) in ether (12 ml). After the mixture had been kept stirring overnight, white precipitates were removed by filtration (1.40 g). The filtrate was distilled and the fraction boiling at 80—130 °C was collected. The distillate was then subjected to preparative glc to yield pure cyclohexene oxide. Cyclohexene oxide isolated was identical (IR, NMR and mass spectra) with that prepared by independent synthesis.

By a separate experiment, the yield of the cyclohexene oxide was determined to be 68% by glc analysis using tetraline as an internal standard. Similarly, 2,5-hexanediol and 1-phenyl-1,2-ethanediol were converted into 2,5-dimethyloxolane and 2-phenyloxirane in 48% and 27% yields, respectively.

*Reaction of Benzoic Anhydride with **1** and **2**.* To a solution of benzoic anhydride (226 mg, 1 mmol) and **2** (262 mg, 1 mmol) in THF (2 ml) was added dropwise over a period of 1 hr at room temperature a solution of **1** (174 mg, 1 mmol) in THF (1 ml). After the solution had been kept stirring overnight, **7** was isolated in an 80% yield by preparative tlc (ether–petroleum ether 1 : 1). The material was recrystallized from ether–petroleum ether, mp 82—83 °C: IR (KBr) cm^{-1} 1750, 1710 (C=O); NMR (CCl_4) δ 1.05 (t, 6H), 4.13 (q, 4H), 7.1—8.0 (m, 10 H).

References

1) Part II: M. Wada, T. Sano, and O. Mitsunobu, This Bulletin, **46**, 2833 (1973).

2) a) O. Mitsunobu, K. Kato, and J. Kimura, *J. Amer. Chem. Soc.*, **91**, 6510 (1969). b) O. Mitsunobu, J. Kimura, and Y. Fujisawa, This Bulletin, **45**, 245 (1972).

3) a) O. Mitsunobu, M. Wada, and T. Sano, *J. Amer. Chem. Soc.*, **94**, 679 (1972). b) H. Morimoto, T. Furukawa, K. Miyajima, and O. Mitsunobu, *Chem. Lett.*, **1973**, 821.

4) A. K. Bose, B. Lal, W. A. Hoffman III, and M. S. Manhas, *Tetrahedron Lett.*, **1973**, 1619.

5) O. Mitsunobu and M. Eguchi, This Bulletin, **44**, 3427 (1971).

6) a) J. P. H. Verheyden and J. G. Moffatt, *J. Org. Chem.*, **35**, 2319, 2868 (1970); **37**, 2289 (1972). b) M. Wada and O. Mitsunobu, *Tetrahedron Lett.*, **1972**, 1279.

7) E. L. Eliel in "Steric Effects in Organic Chemistry," ed. by M. S. Newman, John Willey & Sons, Inc.; Maruzen Co. Ltd., Tokyo, (1956), p. 61.

8) Recently, stable phosphoranes were prepared by the reaction of **2** with uridine and **1**, or with tetramethyl-1,2-dioxetane. J. Kimura, Y. Fujisawa, T. Sawada, and O. Mitsunobu, *Chem. Lett.*, **1974**, 691: P. D. Bartlett, A. L. Baumstark, and M. E. Landis, *J. Amer. Chem. Soc.*, **95**, 6486 (1973).

9) I. Kuwajima and T. Mukaiyama, *J. Org. Chem.*, **29**, 1385 (1964).

10) J. C. Kauer, "Organic Syntheses," Coll. Vol. IV, p. 411 (1963).

11) J. M. Sprague and H. Adkins, *J. Amer. Chem. Soc.*, **56**, 2669 (1934).

12) E. Katzschmann, G. P. 1198342; *Chem. Abstr.*, **63**, 13162 (1965).

13) L. F. Fieser and M. Fieser, "Advanced Organic Chemistry," Reinhold Publishing Co., New York, (1961), p. 191.

14) A. Roebuck and H. Adkins, "Organic Syntheses," Coll. Vol., III p. 217 (1955).

15) A. Gagis, A. Fusco, and J. T. Benedict, *J. Org. Chem.*, **37**, 3181 (1972).