Isomeric Mixture Analysis of Some Ring-opening Reactions of Styrene Oxide

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Mixtures of ring-opened and other products of reactions of acetic or benzoic acids, or ethanol, or phenol with styrene oxide under various conditions can be qualitatively and quantitatively analyzed without isolation of the components by the use of n.m.r. This method, in the case of the ester products, avoids confusing the initial ring-opening result with the results observed after subsequent acyl migrations which readily occur in this type of system.

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Le mélange des produits ouverts et des autres produits de réaction de l'acide acétique ou de l'acide benzoïque ou de l'éthanol ou des phénols avec l'oxyde de styrène sous diverses conditions expérimentales peut être analysé quantitativement et qualitativement sans isoler les produits grâce à la r.m.n. Cette méthode dans le cas des esters évite de confondre le résultat de l'ouverture initiale du cycle avec les résultats obtenus après la migration subséquente du groupe acyle qui se produit facilement dans ce type de système. [Traduit par le journal]

Introduction

Synthetic (1, 2) and kinetic (3) studies of the ring-opening reactions of styrene oxide have gone a long way towards elucidation of the mechanism. The difficulty in studies of this type has been the qualitative and quantitative analysis of the often complex product mixtures obtained (4, 5). Isomer mixtures are frequently obtained on the opening of unsymmetrical epoxides (*e.g.* 1, 6) and the first-formed isomer mixture with carboxylic acids may undergo ready acyl migration with heat or even mildly acidic or alkaline conditions, as seen with glyceryl part esters (7). Concomitant epoxide rearrangements in the presence of acid or base give by-products which complicate ring-opened product recovery and analysis (8, 9), and low polymer oils from condensation of two or three units of original epoxide (5, 10) also contribute to the difficulties. Complicating factors such as these confused much of the early work with epoxide ring-opening reactions (4, 5).

We have examined the use of n.m.r. as a tool for qualitative and quantitative use in a study of some ring-opening reactions of styrene oxide. This method appeared to offer simplicity and speed of analysis, and also to make possible the determination of initial product ratios in the presence of extraneous material and prior to possible subsequent rearrangements. Not only would success with this procedure permit analysis in appropriate systems without isolation of the components but it would avoid errors of interpretation caused by chemical changes introduced by the work-up or derivitization techniques themselves.

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Experimental

Styrene oxide was purchased from Aldrich Chemical Company and vacuum redistilled (fraction boiling at 74.5–75°/11 mm) immediately prior to use. Preparative details are given in Table 1, with footnoted elemental analyses by A. B. Gygli and Associates, Toronto, for new compounds. Nuclear magnetic resonance spectra were obtained on 10% solutions in deuteriochloroform at room temperature on Varian A-60 and HA-60 instruments. Shifts are reported as centers of the respective multiplets from internal tetramethylsilane (Table 2). Isomer mixtures were identified by n.m.r. and quantified by calculation using integrals of the same groupings of each isomer.

Results and Discussion

Styrene oxide was chosen as a sample substrate for this study because it was an unsymmetrical epoxide expected to give ring-opened products with relatively simple n.m.r. resonance patterns for the aliphatic protons. And styrene oxide is no different from other epoxides in the appearance of conflicting reports on its behavior during ring-opening reactions. With acetic acid, for instance, Hickinbottom and Hogg (10) claim that attack is predominantly at the primary

TABLE 1. Summary of ring-opening reactions of styrene oxide, plus derivative preparations and disproportionations

Product (average yield)	Reagents	Reaction conditions	Isomer ratios (mol%): 2° alcohol, 1° derivative	Isomer ratios (mol%): 1° alcohol, 2° derivative
2-Acetoxy-2-phenylethanol **3***a* (50%)	Acetic acid + styrene oxide	(*a*) Neat, 24 h at 3° + 24 h at 23°; unreacted starting materials:	0	100
		(*i*) removed via cold wash;*	0	100
		(*ii*) distilled off at <32°;	5	95
		(*iii*) product from above distilled (93–98°/0.3 mm)	50	50
		(*b*) Neat, 23° for 7 days	50	50
2-Acetoxy-1-phenylethanol **4***a* (75%)	1-Phenyl-1,2-ethanediol **1**, pyridine, + acetyl chloride	(*a*) In benzene, 1 h at 5–10° + 1 h at 25°;	95	5
		(*i*) above product distilled (112–113°/1 mm);	70	30
		(*ii*) distilled product heated at 117°/8 days	53	47
2-Benzoyloxy-1-phenylethanol **4***b* + 2-Benzoyloxy-2-phenylethanol **4***a* (total = 15%)	Benzoic acid + styrene oxide	(*a*) In ethanol, 1.5 h at 85° + 14 h at 23°, cold wash* work-up	70†	30†
		(*b*) In ethanol, 48 h at 25°;	80†	20†
		(*i*) product distilled (157°/0.1 mm) m.p. 67.5–70° (lit. (1) m.p. 62–64°);	80	20
		(*ii*) evaporated filtrate from crystallization	62	38
		(*c*) Neat, 2.5 h at 100° + product distilled (152–7°/0.1 mm)	70	30
2-Benzoyloxy-1-phenylethanol **4***b* (50%)	**1**, pyridine, + benzoyl chloride	(*a*) In benzene, 2.3 h at 20°	100	0
		(*b*) In benzene, 1 h at 80°	100	0
2-Ethoxy-1-phenylethanol **7***a* + 2-Ethoxy-2-phenylethanol **6***a* (total = 30%)	Ethanol (excess) + styrene oxide	(*a*) Neat, 48 h at 85°, distilled (119–123°/9.5 mm); 20% of styrene oxide polymerized	40	60
2-Ethoxy-2-phenylethanol **6***a* (30%)	Ethanol (excess), styrene oxide (30 g), + benzoic acid (61 g)	(*a*) Neat, 48 h at 23°, with benzoic acid "catalysis"	0	100
		(*b*) Boiled 1.5 h with benzoic acid "catalysis", wash* recovery;	0	100
		product distilled (113–115°/8 mm)‡	0	100

TABLE 1. (*Concluded*)

Product (average yield)	Reagents	Reaction conditions	Isomer ratios (mol%): 2° alcohol, 1° derivative	Isomer ratios (mol%): 1° alcohol, 2° derivative
2-Ethoxy-2-phenylethyl benzoate (60%)	**6***a*, pyridine, + benzoyl chloride	Boiled 1 h in benzene, isolated by washing,* plus distillation (170–176°/2.3 mm); crystallized, hexane, m.p. 39–40°§	— — 0	— — 100
2-Phenyl-2-iodoethanol (50%)	hydriodic acid + styrene oxide	In petroleum ether, 0–5°/1 h, wash purification (11), pale yellow solid, m.p. 60–65° (lit. (11) m.p. 77.5°)	0	100
2-Phenoxy-2-phenylethanol **6***b* (10%)	phenol + styrene oxide	In benzene, 2.5 h at 85°, aqueous carbonate wash + distillation (175°/0.1 mm); recryst. 4×, ether–hexane, m.p. 77–79° (lit. (12) 62–63.5°)‖	0 —	100 —
2-Phenoxy-2-phenylethyl benzoate (55%)	**6***b*, pyridine, + benzoyl chloride	Boiled 1 h in benzene, isolated by washing,* recryst. 2×, methanol, m.p. 78–80°	—	—
Derivatives of 1-phenyl-1,2-ethanediol **1**¶				
-diacetate (80%)	**1**, pyridine, + acetyl chloride	In boiling benzene, wash* work up, distilled (107–107.5°/0.5 mm) (lit. (13) b.p. 107–112°/0.4 mm)	—	—
-dicrotonate (35%)	**1**, pyridine, + crotonoyl chloride	As above, b.p. 127–131°/0.05 mm; about 10% crotonic anhydride also obtained	—	—
-dibenzoate (90%)	**1**, pyridine, + benzoyl chloride	As above but crystallized from benzene, m.p. 91.5–93° (lit. (14) m.p. 93.5–95°)	—	—

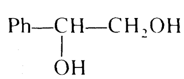
*Dilution with cold CH_2Cl_2, followed by ice water, cold aqueous $NaHCO_3$, and ice water washes, drying (Na_2SO_4), and solvent removal under reduced pressure.
†About 25% yield ring-opened products, plus prototropic shift to yield observed phenylacetaldehyde.
‡Anal. Calcd. for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.21; H, 8.45. Isomeric assignment confirmed by benzoylation.
§Anal. Calcd. for $C_{17}H_{18}O_3$: C, 79.22; H, 5.70. Found: C, 79.21; H, 5.67.
‖Anal. Calcd. for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59. Found: C, 78.44; H, 6.62.
¶Diacrylate preparations gave insoluble red polymers.

TABLE 2. Nuclear magnetic resonance chemical shifts and calculated shift differences for some 1-phenyl-1,2-ethanediol derivatives*

	Proton shifts p.p.m. (δ)		$\delta_{diester} - \delta_{monoester}$		$\delta_{derivative} - \delta_{diol}$	
Compound	Methine	Methylene	Methine	Methylene	Methine	Methylene
1-Phenyl-1,2-ethanediol	4.67	3.56	—	—	—	—
Acetates						
diacetate	5.97	4.25	—	—	1.30	0.69
sec. mono, **3***a*	5.92	3.88	0.05	0.37	1.25	0.32
prim. mono, **4***a*	4.87	4.18	1.10	0.07	0.20	0.62
Benzoates						
dibenzoate	6.41	4.70	—	—	1.74	1.14
sec. mono, **3***b*	5.97	3.68	0.44	1.02	1.30	0.12
prim. mono, **4***b*	4.97	4.33	1.44	0.37	0.30	0.78
Monoethyl ethers:						
sec., **6***a*	4.39	3.69	—	—	−0.28	0.13
prim., **7***a*	4.77	3.40	—	—	0.10	0.16
sec. ether, prim. benzoate	4.67	4.45	1.74	0.25	—	—
Monophenyl ethers:						
sec., **6***b*	5.13	3.78	—	—	−0.46	−0.22
sec. ether, prim. benzoate	5.56	4.65	0.85	0.05	—	—
2-Phenyl-2-iodoethanol	5.13	3.91	—	—	−0.46	−0.35
Styrene oxide	3.74	2.83				

*Integration of relative peak areas in all cases agreed with the assignments given.

carbon to give 2-acetoxy-1-phenylethanol **4***a*, whereas others (1, 6) claim that the secondary carbon is preferentially attacked giving largely 2-acetoxy-2-phenylethanol **3***a*. The present study finds support for the latter claim and provides a method which may prove helpful in other systems.



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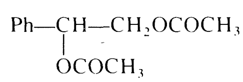
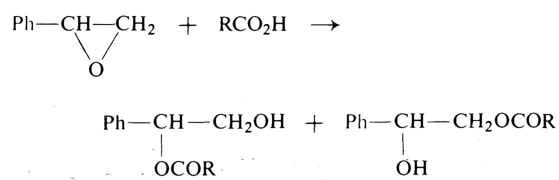


2

Nuclear magnetic resonance chemical shifts were determined for the methine and the methylene protons of, for example, styrene glycol, **1**, and styrene glycol diacetate, **2**. Subtracting the shifts of the methine protons of the diol **1** from the diester **2**, and subtracting the methylene protons in the same way, we obtained shift differences of 1.30 and 0.69, respectively (Table 2).

For a styrene glycol monoacetate of unknown ester orientation, relative integrals establish whether a multiplet is arising from the methine or the methylene group. Noting the respective shifts and carrying out the same type of operation as outlined above but now between the monoester **3***a* and the diester **2**, we obtain shift



3 **4**

a R = CH_3

b R = Ph

differences for **3***a* of 0.05 and 0.37 for the methine and the methylene groups, respectively. This result immediately suggests that ester attachment is on methine. To confirm this, repeating the procedure, but now between monoester **3***a* and diol **1** we obtained shift differences of 1.25 for the methine proton and 0.32 for the methylene protons, indicating that hydroxyl in **3***a* is on methylene. The evidence that both operations on **3***a* agreed and that duplicating the result on **4***a* gave the opposite ester orientation, strongly supported the use of the method for this purpose. With benzoate esters the method was found to be equally suitable.

With monoethers, where the deshielding effect of an aryl or alkyl group was much less different from hydrogen than the deshielding effect of an acyl group, the distinction was far less marked than with the monoesters. But the method still gave the correct result, demonstrated by esterification of the free hydroxyl and repeating the calculations based on ester differences. Since the ethers obtained by epoxide opening are much less prone to disproportion, even if ester preparation is necessary to distinguish ether orientation in particular case, it does not seriously detract from the usefulness of the method.

The method may be used to simultaneously determine each component (mol%) of mixtures of acetic acid, styrene oxide, and the two monoesters because the respective multiplets are well separated. And in ester systems at least, the side reactions of styrene oxide leading to phenylacetaldehyde or polymeric products **5** can again be separated from the desired results

$$\mathrm{+\!O{-}CHPh{-}CH_2\!+_{\!n}O{-}}$$

5

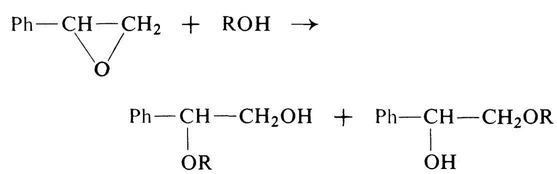
because the deshielding effects of aldehyde and ether functions differ sufficiently from the compounds of interest.

Reacting styrene oxide with acetic acid at room temperature gave mixtures of the two monoacetates **3***a* and **4***a* (Table 1), in accordance with that found earlier by Berti *et al.* (1) and Cohen *et al.* (6), and not 2-acetoxy-1-phenylethanol (10). At about +3° only 2-acetoxy-2-phenylethanol **1***a* was obtained, the first time this has been demonstrated and vindicating suggestions by others (1, 6).

Reacting 1-phenyl-1,2-ethanediol with acetyl chloride yielded 2-acetoxy-1-phenylethanol contaminated with only about 5% of the other isomer (Table 1). Distillation only decreased the proportion of 2-acetoxy-1-phenylethanol present to 70%, and further heating established that the equilibrium lay at near a 50:50 mixture.

At elevated temperatures, benzoic acid plus styrene oxide gave a mixture (about 70% primary, **2***b*) of monobenzoate esters, not significantly changed by reaction at room temperature (*cf.* 1). Pure 2-benzoyloxy-1-phenylethanol was obtained directly via 1-phenyl-1, 2-ethanediol and benzoyl chloride (Table 2) but attempts to obtain 2-benzoyloxy-2-phenylethanol in pure form through silver benzoate plus 2-phenyl-2-iodoethanol or by fractional crystallization of the potassium xanthate salts of the mixed monoesters were unsuccessful.

The monoether 2-ethoxy-2-phenylethanol **6***a*, was isolated pure as a co-product. This finding supports the two earlier reports by Chapman *et al.* (3) and Winstein and Ingraham (15) claiming purely secondary ether formation on strong acid catalyzed ring opening of styrene oxide with methanol and does not correspond with Reeve and Christoffel's (16) finding that mixtures resulted. In the absence of benzoic acid 60% 2-ethoxy-2-phenylethanol **6***a* was formed.



6 **7**

a R = CH_3CH_2

b R = Ph

With phenol in boiling benzene 100% attack at the secondary carbon of styrene oxide was obtained, near the 90% **6***b* that was found by Guss (17) for this reaction. The initial product, 2-phenoxy-2-phenylethanol **6***b*, was not prone to rearrangement.

The halogen acid ring-opened styrene oxide, which had been previously characterized (11) as 2-phenyl-2-iodoethanol, was also found to fit the assignment scheme quite well.

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