Base-Induced Cyclization Reactions of Propargyloxypropanol and the 3-(2-Haloallyloxy)propanols[1]

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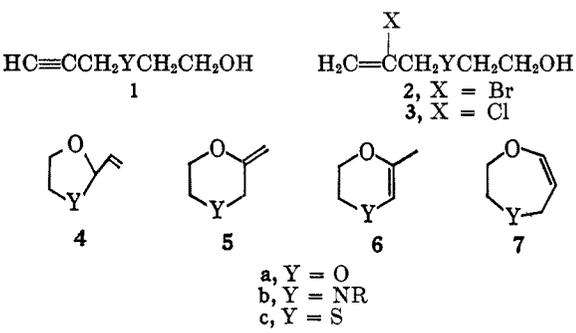
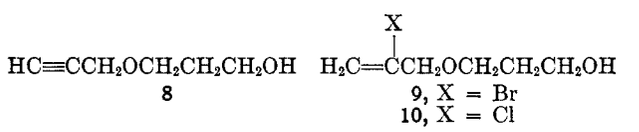
Treatment of 3-propargyloxypropanol (**8**) or the 3-(2-haloallyloxy)propanols (**9** and **10**) with aqueous sodium hydroxide or with potassium *t*-butoxide in *t*-butyl alcohol gave 2-vinyl-1,3-dioxane (**11**) as the only cyclic product. With potassium hydroxide in *t*-butyl alcohol or triglyme, or with sodium hydroxide in dimethyl sulfoxide, the hydroxypropyl ethers **8–10** gave mixtures of **11** and 1-methyl-3,7-dioxacycloheptene (**12**). As the solvent was changed from *t*-butyl alcohol to dimethyl sulfoxide to triglyme, the **11**:**12** ratio decreased markedly. These reactions were compatible with a mechanistic scheme analogous to that used to explain the base-induced cyclization reactions of propargyloxyethanol (**1a**).

In previous studies directed toward determining the scope and limitations of base-induced cyclization reactions of propargyl and 2-haloallyl compounds,[2-4] we have examined the behavior of N-alkyl-N-propargylethanolamines (**1b**),[2] propargyloxyethanol (**1a**),[3] 2-propargylthioethanol (**1c**),[4] and their 2-haloallyl analogs (**2** and **3**). Reactions of the hydroxyethyl ethers **1a**, **2a**, and **3a** proved to be particularly complex in that they gave three and usually four cyclic products (**4a**, **5a**, **6a**, and **7a**) in varying amounts depending on the conditions used. In contrast, the hydroxyethyl sulfides **1c**, **2c**, and **3c** gave only one cyclic product, 2-methyl-1,4-oxathiene (**6c**). Also, essentially pure 4-alkyl-2-methylenemorpholine (**5b**) could be obtained by treating the corresponding N-alkyl-N-propargylethanolamine (**1b**) or N-alkyl-N-(2-haloallyl)ethanolamine (**2b** and **3b**) with sodium hydroxide in water, and essentially pure 3-alkyl-2-vinyloxazolidine (**4b**) could be obtained by treating the corresponding **1b**, **2b**, or **3b** with sodium hydroxide in an aprotic solvent.

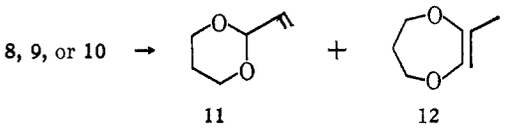


Related mechanistic schemes have been proposed to explain the behavior of the hydroxyethylpropargyl and 2-haloallyl compounds, and differences in the mode of cyclization of the amines, ethers, and sulfides have been rationalized on the basis of electronic and steric reasons.

It appeared that a suitable test of these mechanistic schemes could be obtained by examining the behavior, under similar reaction conditions, of one or more of the corresponding hydroxypropyl compounds. Although the reactions of the hydroxyethyl ethers **1a**, **2a**, and **3a** gave the most complex mixtures of cyclic products, this study proved to be the most informative concerning the mechanisms by which the hydroxyethyl compounds undergo cyclization reactions. Considering this, we prepared 3-propargyloxypropanol (**8**) and the corresponding 2-haloallyl compounds (**9** and **10**) and studied their base-induced cyclization reactions.



Treatment of **8–10** with aqueous sodium hydroxide or with potassium *t*-butoxide in *t*-butyl alcohol gave only one cyclic product, 2-vinyl-1,3-dioxane (**11**). On treatment with sodium hydroxide in dimethyl sulfoxide or potassium hydroxide in *t*-butyl alcohol or triglyme, **8–10** gave mixtures of **11** and a second cyclic product, 1-methyl-3,7-dioxacycloheptene (**12**). Identification of **11** was accomplished by comparing it with material prepared from acrolein and 1,3-propanediol.[5] Tentative identification of **12** was made on the basis of its infrared and nmr spectra, and its structure was confirmed by means of its reaction with aqueous mercuric acetate, which gave methylglyoxal and 1,3-propanediol.[6]



Interestingly, the reaction of 3-(2-chloroallyloxy)-propanol (**10**) with an equal molar amount of sodium hydroxide in dimethyl sulfoxide gave 3-allenyloxypropanol (**13**) as the major product. Unfortunately, the **13** was not obtained free of propargyloxypropanol (**8**).

$$H_2C{=}C{=}CHOCH_2CH_2CH_2OH$$

13

Summarized in Table I are the yields and compositions of cyclic ethers obtained from reactions of the hydroxypropyl ethers with base. Control experiments carried out in *t*-butyl alcohol and in dimethyl sulfoxide showed that the products are stable under the reaction conditions.

The results obtained with 3-propargyloxypropanol (**8**) are best explained on the basis of a sequence of re-

(1) This investigation was supported by Grant GM-10606 from the National Institute of General Medical Sciences of the U. S. Public Health Service.

(2) A. T. Bottini, J. A. Mullikin, and C. J. Morris, *J. Org. Chem.*, **29**, 373 (1964).

(3) A. T. Bottini, F. P. Corson, and E. F. Böttner, *ibid.*, **30**, 2988 (1965).

(4) A. T. Bottini and E. F. Böttner, *ibid.*, **31**, 385 (1966).

(5) R. F. Fischer and C. W. Smith, *ibid.*, **25**, 319 (1960).

(6) The experiments used to establish the structure of **12** were patterned after those used by R. K. Summerbell, G. H. Kalb, E. S. Gram, and A. L. Allred [*ibid.*, **27**, 4461 (1962)] to establish the structure of 2-methyl-1,4-dioxene (**6a**).

TABLE I

YIELDS AND COMPOSITIONS OF CYCLIC ETHERS FROM REACTIONS OF HYDROXYPROPYL ETHERS WITH BASE[a]

Ether	Solvent	Base	Temp, °C[b]	Time, hr	Yield, %[c]	—Composition, %— 11	12
8	H_2O	NaOH	100	8	~1[d]	>98	<2
9	H_2O	NaOH	100	22	~1[e]	>98	<2
10	H_2O	NaOH	100	22	0.3[f]	>98	<2
8	*t*-BuOH	KOH	80	12	10	74	26
8	*t*-BuOH	*t*-BuOK	80	5	56	>98	<2
9[g]	*t*-BuOH	*t*-BuOK	80	12	42	>98	<2
10	*t*-BuOH	*t*-BuOK	80	16	21	>98	<2
8	DMSO	NaOH	80	1.5	26	55	45
9	DMSO	NaOH	80	3	22	55	45
10[h]	DMSO	NaOH	80	3	19	62	38
8	Triglyme	KOH	180	0.3	49	18	82
9	Triglyme	KOH	180	0.3	17	39	61

[a] Typical procedures are given in the Experimental Section. [b] ±5°. [c] Not corrected for recovered starting material. [d] The recovered **8** (69%) contained no detectable **13**. [e] A 55% yield of **8** was also obtained. [f] A 19% yield of **8** was also obtained. [g] A reaction of **9** in *t*-BuOH with *t*-BuOK at 80° for 8 hr with an initial *t*-BuOK/**9** mole ratio of 0.85 gave a 66% yield of **8**. The **8** contained no detectable (<3%) **13**. [h] A reaction of **10** in DMSO with NaOH at 70° for 6 hr with an initial NaOH/**10** mole ratio of 1.0 gave a 38% yield of a 70:30 mixture of **13** and **8**. The reaction and work-up are described in the Experimental Section.

actions analogous to that proposed to explain the reactions of propargyloxyethanol (**1a**) with base.[3] The first step in this sequence is formation of 3-allenyloxypropanol (**13**) by base-induced prototropic rearrangement of **8**. Two reactions of **13** can occur: cyclization *via* its alkoxide to 2-vinyl-1,3-dioxane (**11**); or prototropic rearrangement to 3-(1-propynyloxy)propanol (**14**), which can cyclize *via* its alkoxide to 1-methyl-3,7-dioxacycloheptene (**12**). As was observed for **1a**,[3] the cyclization reaction of the 1-propynyl ether becomes increasingly important as the solvent is changed from water to dimethyl sulfoxide to triglyme.

The most notable difference in reactivity of 3-propargyloxypropanol (**8**) and propargyloxyethanol (**1a**) was with aqueous sodium hydroxide. Whereas **1a** gave three cyclic products (**4a**, **5a**, and **7a**) in over 50% yield, **8** gave only one, 2-vinyl-1,3-dioxane (**11**), in ≈1% yield. The major products from **1a** in water are 2-methylene-1,4-dioxane (**5a**) and 3,6-dioxacycloheptene (**7a**), which are formed by nucleophilic addition of alkoxide to the acetylenic carbons of **1a**. Analogous cyclization reactions of **8** would give 2-methylene-1,4-dioxacycloheptane (**15**) and 3,7-dioxacyclooctene (**16**). As **15** and **16** are likely to be stable under the reaction conditions, and as not even a trace of either compound was detected, it can be concluded that their rates of formation are much slower than those of their next lower homologs. The simplest explanation for this is that **15** and **16** are more strained than their next lower homologs and that some of this greater strain is reflected in the transition states leading to their formation.

We extended our studies of the effect of solvent on the course of cyclization reactions of propargyl- and 2-haloallyl compounds by employing *t*-butyl alcohol as a solvent for reactions of **8**–**10**. From consideration of other work,[7,8] it seemed likely that the rates of prototropic rearrangement[7] and the effective basicity (and nucleophilicity)[8] of alkoxide in *t*-butyl alcohol would be greater than in water but less than in dimethyl sulfoxide. Therefore, it seemed reasonable to expect that the product composition obtained using *t*-butyl alcohol would be intermediate between those obtained in the other two solvents. When potassium hydroxide was used as the base, this expectation was realized. When potassium *t*-butoxide was used instead of potassium hydroxide, the yield was increased from 10 to 56%, and the product composition was changed from 74% 2-vinyl-1,3-dioxane (**11**) and 26% 1-methyl-3,7-dioxacycloheptene (**12**) to >98% **11**. The large increase in yield can be ascribed to the faster rate of rearrangement of 3-(propargyloxy)propanol (**8**) to 3-(allenyloxy)propanol (**13**) that results from use of the stronger base. The change of base from hydroxide to *t*-butoxide can also be expected to cause a much greater percentage of **13** to exist in the form of its alkoxide, and this is the most likely cause of the enhancement of the rate of ring closure of **13** to **11** relative to its rate of rearrangement to 3-(1-propynyloxy)-propanol (**14**).

The product composition from reactions of the 3-(2-haloallyloxy)propanols in water, *t*-butyl alcohol, and dimethyl sulfoxide were nearly the same as those obtained from 3-(propargyloxy)propanol (**8**). From this, we conclude that the principal reaction of the 2-haloallyl compounds in these solvents is dehydrohalogenation to the propargyl compound. The initial reaction of 3-(2-bromoallyloxy)propanol (**9**) in triglyme also appears to be dehydrobromination to **8**. If **9** had undergone elimination to 3-(allenyloxy)propanol (**13**) or prototropic rearrangement to a 2-bromopropenyl ether (followed by elimination to **13** or **14**), this would be expected to give a greater amount of 1-methyl-3,7-dioxacycloheptene (**12**) in the product rather than the observed smaller amount of **12**. Similar differences were observed in the product compositions obtained from reactions of the homologous hydroxyethyl ethers in triglyme,[3] and these differences were explained as being due to a change in medium that is the result of water formed during the dehydrohalogenation reaction.

(7) See C. C. Price and W. H. Snyder, *J. Am. Chem. Soc.*, **83**, 1773 (1961); *J. Org. Chem.*, **27**, 4639 (1962).

(8) See D. J. Cram, B. Rickborn, and G. R. Knox, *J. Am. Chem. Soc.*, **82**, 6412 (1960); D. J. Cram, B. Rickborn, C. A. Kingsbury, and P. Haberfield, *ibid.*, **83**, 3678 (1961).

Experimental Section

Melting points and boiling points are uncorrected. Infrared spectra were obtained with a Beckman IR-4 spectrophotometer. Nmr spectra were determined of compounds as 20% solutions in

carbon tetrachloride at 56.4 Mc with a Varian Associates HR-60 system equipped with electronic integrator and base-line stabilizer. Resonance frequencies in nmr spectra were determined relative to internal tetramethylsilane (TMS) using the side-band technique with a Packard CD-200 audiooscillator and are reported in cycles per second downfield from the TMS resonance. Gas–liquid partition chromatograms (glpc) were obtained using either a Loe Model 1 Chromat-O-Flex or a Wilkens Model A-700. Microanalyses were performed by Mr. V. H. Tashinian, Berkeley, Calif.

3-Hydroxypropyl Ethers 8–10.—Employing a procedure patterned after that described for the preparation of 2-(2-bromoallyloxy)ethanol,[3] 23 g (1.0 g-atom) of sodium, 300 g of 1,3-propanediol, and 119 g (1.0 mole) of propargyl bromide were used to prepare 45 g (39%) of 3-propargyloxypropanol (**8**), bp 90° (15 mm), $n^{25}D$ 1.4492.

Anal. Calcd for $C_6H_{10}O_2$: C, 63.14; H, 8.83. Found: C, 62.90; H, 8.73.

3-(2-Bromoallyloxy)propanol (**9**), which was prepared in a similar manner in 47% yield, had bp 94–95° (0.8 mm), $n^{25}D$ 1.4841.

Anal. Calcd for $C_6H_{11}BrO_2$: C, 36.94; H, 5.68. Found: C, 36.80; H, 5.70.

3-(2-Chloroallyloxy)propanol (**10**), which was also prepared in a similar manner in 72% yield, had bp 67–70° (0.5 mm), $n^{24}D$ 1.4600.

Anal. Calcd for $C_6H_{11}ClO_2$: C, 47.85; H, 7.36; Cl, 23.54. Found: C, 48.37; H, 7.62; Cl, 23.17.

The infrared and nmr spectra of **8–10** were in accord with the assigned structures.

Identification of the Cyclic Ethers 11 and 12.—A mixture of 20 ml of triglyme and 2.8 g (0.05 mole) of coarsely powdered potassium hydroxide was placed in a four-necked flask fitted for distillation and equipped with stirrer, dropping funnel, and nitrogen inlet tube. The nitrogen flow was started, the system was evacuated to 90 mm, and the vigorously stirred mixture was heated with an oil bath held at 180°. 3-Propargyloxypropanol (**8**, 11.4 g, 0.10 mole) was added dropwise in 10 min. During the addition, distillation occurred, and 19 g of distillate was collected in a cooled receiver. The distillate was redistilled through a semimicro Vigreux column, and the fraction with bp 50–65° (28 mm), $n^{25}D$ 1.4492, was collected. The yield was 5.6 g (49%). Analysis by means of glpc using a 0.25 in. × 15 ft column packed with Cyanosilicon XF-1150 on Chromasorb W-HMDS, indicated that the product was a 5.6:1.0 mixture of two components, and separation was accomplished by preparative-scale glpc on the same column at 112°.

The minor component, identified as 2-vinyl-1,3-dioxane (**11**), had retention times on the Cyanosilicon-packed column and a 0.25 in. × 15 ft column packed with Carbowax 20M (alkaline) on firebrick that were indistinguishable from those of **11**, bp 70–75° (48 mm), $n^{24}D$ 1.4417 [lit.[5] bp 65–66° (44 mm), $n^{20}D$ 1.4438], prepared from acrolein and ethylene glycol. In addition, the infrared and nmr spectra of the minor component were indistinguishable from those of **11** prepared from acrolein and ethylene glycol. The nmr spectrum of **11** was found to consist of numerous lines from 371 to 287 cps (3.74 ± 0.16 H, CH_2=CHCH), a multiplet from 255 to 214 cps (4.00 ± 0.10 H, CH_2O), and two discernible multiplets from 157 to 110 and from 103 to 81 cps (2.00 H, CCH_2C).

The major component was identified as 1-methyl-3,7-dioxacycloheptene (**12**). The infrared spectrum of **12** was found to possess a band at 1685 cm^{-1}, indicating the presence of a polar carbon–carbon double bond. The nmr spectrum of **12** consists of a quartet ($J \approx 1.2$ cps) centered at 330 cps (=CH), an apparent quartet ($J_{ap} \approx 5.5$ cps) centered at 240 cps (CH_2O), an apparent quintet ($J_{ap} \approx 5.6$ cps) centered at 131 cps (CCH_2O), and a doublet ($J \backsimeq 1.2$ cps) at 107 cps. The purest sample of **12** had bp 51° (25 mm).

Anal. Calcd for $C_6H_{10}O_2$: C, 63.14; H, 8.83. Found: C, 62.71; H, 8.50.

A mixture of 114 mg (1 mmole) of **12**, 351 mg (1 mmole) of mercuric acetate dihydrate, and 2 ml of water was shaken at 25° for 30 min.[6] The mercury that formed (175 mg, 88%) was collected, and the filtrate was divided into two equal parts. The first part was used to prepare methylglyoxal phenylosazone (85 mg, 67%), mp 140–142° (lit.[6] mp 144.5–146°); the second part was used to prepare the dibenzoate ester of 1,3-propanediol (15 mg, 11%), mp 52.5–53.5°, mmp 52.5–53.5° with dibenzoate prepared from 1,3-propanediol.

Reactions of 8–10 with Base.—Each reaction of **9** or **10** that gave one or both of the cyclic ethers was carried out using at least one more equivalent of base per mole of hydroxypropyl ether than was used for the similar reaction of **8**. Product analysis was accomplished by means of glpc analysis using the Cyanosilicon XF-1150 column, and this analysis was substantiated by examination of either the infrared or nmr spectrum of the distilled product.

Reactions carried out in water and in dimethyl sulfoxide were patterned after procedures described for reactions of the corresponding hydroxyethyl ethers.[3] A typical reaction carried out in triglyme was described in the preceding section.

The following is typical of reactions carried out in *t*-butyl alcohol. A solution prepared from 150 ml of *t*-butyl alcohol, 19 g (0.17 mole) of potassium *t*-butoxide, and 15.0 g (0.077 mole) of **9** was heated at 80° for 12 hr. The mixture was cooled, and 150 ml of ether and 250 ml of water were added. The phases were separated, and the aqueous solution was extracted twice with 100-ml portions of ether. The extracts were combined, washed with saturated sodium chloride solution, dried with magnesium sulfate, and distilled. The fraction with bp 67–68° (40 mm), $n^{27}D$ 1.4391, weighed 3.7 g (42%), and was >98% 2-vinyl-1,3-dioxane (**11**).

3-Allenyloxypropanol (13).—A heterogeneous mixture prepared from 15.0 g (0.10 mole) of **10**, 4.0 g (0.1 mole) of sodium hydroxide, and 70 ml of dimethyl sulfoxide was stirred vigorously and heated at 70° for 6 hr. The mixture was allowed to cool, and 100 ml of ether and 100 ml of water were added in that order. The phases were separated, and the aqueous solution was washed successively with water and saturated sodium chloride solution, dried with magnesium sulfate, and distilled. The fraction with bp 66–68° (1 mm) weighed 4.3 g (38%). It possessed a strong band at 1970 cm^{-1}, which indicated the presence of an allene, and a very weak band at 2130 cm^{-1}, which indicated the presence of **8**. The nmr spectrum of the product consisted of the bands characteristic of **8** together with a triplet ($J \approx 6.3$ cps) at 404 cps (=C=C<H), and a doublet ($J \approx 6.4$ cps) at 326 cps (=C=CH_2). Comparison of the relative intensities of the bands due solely to either **8** or **13** indicated the mixture was 30 ± 4% **8** and 70 ± 4% **13**.

Anal. Calcd for $C_6H_{10}O_2$: C, 63.14; H, 8.83. Found: C, 63.62; H, 8.77.

The glpc of the product was in accord with the nmr analysis and showed further that the product consisted of less than 1% of cyclic ethers. Examination of glpc of the lower-boiling fractions of the distillate failed to provide evidence for the presence of either **11** or **12**.

Stability of the Cyclic Ethers.—A mixture of 20 ml of *t*-butyl alcohol, 1.0 g (0.009 mole) of potassium *t*-butoxide, 2.1 g of 3-methylcyclohexanol, and 2.9 g (0.025 mole) of a 52:48 mixture of **11** and **12** was heated at 75° for 5 hr. The mixture was cooled, and 30 ml of ether and 50 ml of water were added. The phases were separated, and the aqueous solution was extracted twice with 30-ml portions of ether. The ether extracts were combined, washed with 30 ml of saturated sodium chloride solution, and dried with magnesium sulfate. Most of the ether and *t*-butyl alcohol was removed by distillation at atmospheric pressure. Glpc analysis of the residue indicated that the relative composition of 3-methylcyclohexanol, **11**, and **12** had not changed.

A mixture of 5.5 g (0.048 mole) of 2-vinyl-1,3-dioxane (**11**), 10 ml of dimethyl sulfoxide, and 1.0 g (0.009 mole) of potassium *t*-butoxide was stirred and heated at 70° for 3 hr. The mixture was cooled, and 50 ml of ether and 50 ml of water were added. The phases were separated, and the aqueous phase was extracted twice with 50-ml portions of ether. The ether extracts were combined, dried with magnesium sulfate, and distilled to give 4.5 g (82% recovery) of **11**, bp 57–58° (29 mm).