product compared with that of pure phthalic anhydride showed it to be 91% pure.[36]

Potassium *t*-Butoxide Isomerization of Methyl Crepenynate (1).—Redistilled *t*-butyl alcohol was partially dried over anhydrous sodium sulfate and decanted. An excess of metallic sodium was added cautiously over a 4-hr. period. The mixture was refluxed for 1 hr. and the *t*-butyl alcohol was distilled. Potassium (1.3 g.) was added slowly to 30 ml. of the dry alcohol, and the mixture was allowed to stand at room temperature overnight. Precautions were taken to exclude moisture throughout this procedure.

The potassium *t*-butoxide in *t*-butyl alcohol reagent (9.0 ml.) was added to a 0.050-g. sample of methyl crepenynate (**1**) and the solution was stored at 1° overnight. The solidified reaction mixture was warmed to room temperature and allowed to stand 4 hr. This solution was diluted with water, acidified with dilute hydrochloric acid, and extracted with ethyl ether. The recovered product (**7**, 0.046 g.) showed strong allenic absorption in the infrared (Figure 1D). Ultraviolet analysis (Figure 2B) gave $\lambda_{\max}^{\mathrm{EtOH}}$ 222 mμ (ε 18,900) and also 268 mμ (ε 3800).

Infrared analysis of the methyl esters of **7** prepared with diazomethane showed that the allenic absorption at 1935 and 874 cm.$^{-1}$ remained unchanged. Analyses of these esters by g.l.c. gave 42% cyclic ester **4** and 49% conjugated trienes on the LAC-2-R 446 column (196°), and 69% cyclic ester and 20% conjugated trienes on the Apiezon L column (250°).

***Rearrangement of Enallene* 7 by Heat.**—The enallenic acid **7** was heated in a nitrogen atmosphere on a steam bath and infrared spectra of the products were determined periodically. The bands at 1935 and 874 cm.$^{-1}$ had completely disappeared after the sample had been heated for 1 hr. and 50 min. and the spectrum of the final material was identical with that of the conjugated trienes **2a–3** from potassium hydroxide isomerization of methyl crepenynate.

Hydrazine Reduction of Rearrangement Products 2a–3.—The partial hydrazine reduction of the conjugated trienes and c.c.d. of the esterified reduction products were done as previously described.[21] Analysis of the esterified reduction mixture by g.l.c. gave the following composition (all components are C_{18}): saturated, 12%; monoenes, 24%; isolated diene, less than 1%; *cis,trans* (*trans,cis*) conjugated diene, 25%; *cis,cis* conjugated diene, 6%; *trans,trans* conjugated diene, 4%; cyclic, 12%; and conjugated triene, 15%.

Quantitative infrared analysis of the monoene fraction (97% monoene by g.l.c.) from c.c.d. showed absorption at 963 cm.$^{-1}$ equivalent to 19.6% of isolated *trans* double bonds calculated as methyl elaidate.[23] The conjugated diene fraction was shown by g.l.c. to contain 69% *cis,trans* (*trans,cis*), 16% *cis,cis*, and 11% *trans,trans* dienes.

Separation of Monoenes 9.—The monoene fraction was separated into a *cis* (**11**) and *trans* (**12**) fraction by preparative t.l.c. on silver nitrate impregnated silica gel G plates as described previously for the hydrazine reduction of α-eleostearic acid.[21] The *trans* fraction contained 15% of *cis* isomers, and the *cis* fraction contained no *trans* isomers. Total recovery from the t.l.c. plates was 91%.

Permanganate–Periodate Oxidation of 11 and 12.—Both the *cis*- and *trans*-monoene fractions were cleaved by permanganate-periodate oxidation in 60% *t*-butyl alcohol as described by von Rudloff.[37] The products were recovered as usual, and the free acids were subjected to analysis by g.l.c. only for identification of the monobasic fragments. Hexanoic, heptanoic, octanoic, nonanoic, and decanoic acids were produced from the *cis*-monoene fraction. The *trans*-monoene fraction yielded all the straight-chain monobasic acids from pentanoic through undecanoic acid. The remaining oxidation products were esterified by refluxing with 1% sulfuric acid in methanol, and the esters were analyzed by g.l.c. for identification and percentages of the various dibasic cleavage fragments. The percentages were converted into the original composition of the monoene fractions (Table I).

Permanganate–Periodate Oxidation of 10.—The conjugated diene fraction **10** was cleaved like the monene fractions, and the products were recovered and analyzed as free acids by g.l.c. This analysis showed that all the straight-chain monobasic acids from butanoic through decanoic were present and that hexanoic and octanoic acids were the major components. The remainder of the cleavage products was esterified by sulfuric acid in methanol, and the esters were analyzed by g.l.c. The percentages of dibasic acid methyl esters were hexanedioate, 1%; heptanedioate, 1%; octanedioate, 34%; nonanedioate, 10%; decanedioate, 42%; undecandieoate, 10%; and dodecanedioate, 2%.

Acknowledgment.—We are grateful to C. R. Smith, Jr., for helpful guidance in portions of the work; to J. W. Hagemann for gas–liquid chromatographic analyses; and to E. Selke and W. K. Rohwedder for the mass spectral analysis.

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[36] M. M. Agarwal and F. Spagnolo, *Anal. Chem.*, **25**, 1412 (1953).

[37] E. von Rudloff, *Can. J. Chem.*, **34**, 1413 (1956).

Base-Induced Cyclization Reactions of Propargyloxyethanol and the 2-Haloallyloxyethanols[1a]

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Cyclization reactions of propargyloxyethanol (**7**) and the 2-haloallyloxyethanols **5** and **6** induced by sodium hydroxide or potassium hydroxide were found to be markedly dependent on solvent. In water, 3,6-dioxacycloheptene (**11**) and 2-methylene-1,4-dioxane (**9**) are the main products; 2-vinyl-1,3-dioxolane (**8**) is also formed. In decalin, dimethyl sulfoxide, and triglyme, **8** and 2-methyl-1,4-dioxene (**10**) are the major products, and only small amounts of **9** and **11** are formed. The mechanisms of formation of **8–11** are discussed.

Treatment of a 2-haloallyl compound with base can bring about one or more of a large number of transformations. Dehydrohalogenation across either the double bond or the single bond of a 2-haloallyl group (a) can occur to give a propargyl group (b) or an allenyl group (c), respectively; the 2-haloallyl group can also undergo prototropic rearrangement to a *cis*- or *trans*-2-halopropenyl group (d). Reactions of the initially formed products can also occur; thus, dehydrohalogenation of d can lead to c or a 1-propynyl group (e), and prototropic rearrangement of the propargyl group (b) can lead to an allenyl group (c), which in turn can undergo protropic rearrangement to e. Further, each unsaturated carbon in a–e is susceptible to attack by a nucleophile. Therefore, a 2-haloallyl compound or a propargyl compound that contains a nucleophilic atom can undergo conceivably a number of base-induced cyclization reactions. From these considerations, we concluded that detailed study of the fate of such 2-haloallyl or propargyl compounds, on treatment with base,

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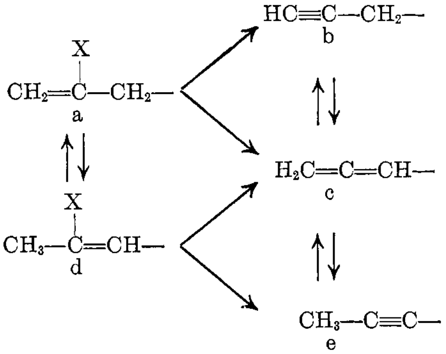
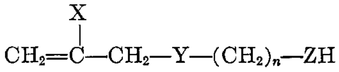
[1] (a) Presented in part at the 145th National Meeting of the American Chemical Society, New York, N. Y., Sept. 1963. This research was supported in part by Grant GM-10606 from the Division of General Medicine of the Public Health Service. (b) National Defense Graduate Fellow.

in addition to offering promise of yielding ready access to a large number of heterocyclic systems, could make possible assessment of the role of the various factors that, combined, determine the relative importance of the competing dehydrohalogenation, prototropic rearrangement, and intramolecular nucleophilic addition reactions. Accordingly, we have undertaken a study of the scope and limitations of reactions with base of compounds that can be represented generally by **1** and **2**.





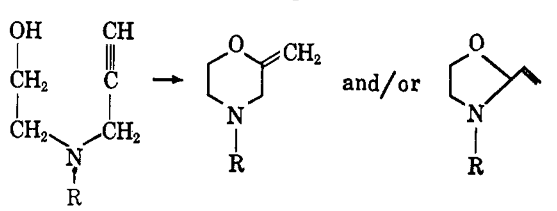
$CH_2{=}\overset{X}{\overset{|}{C}}{-}CH_2{-}Y{-}(CH_2)_n{-}ZH$

1

$HC{\equiv}C{-}CH_2{-}Y{-}(CH_2)_n{-}ZH$

2

Earlier work[2,3] has shown that the mode of cyclization of an N-alkyl-N-propargylethanolamine (**2a**, Y = NR; Z = O; n = 2) induced by sodium hydroxide or potassium hydroxide is markedly dependent on solvent; in water,[3] the only cyclic product obtained is the corresponding 2-methylenemorpholine (**3**), while, in the aprotic solvents toluene,[2,3] dimethyl sulfoxide,[3] or ether, the major and oftentimes sole product is the 2-vinyloxazolidine (**4**). Formation of the 2-methylenemorpholine was shown to occur by nucleophilic addition to acetylenic carbon, and 2-vinyloxazolidine formation was explained as occurring by prototropic rearrangement of **2a** to the corresponding allenic amino alcohol followed by nucleophilic addition at C-1 of the allene moiety. The dependence of reaction path on solvent was rationalized as being due to the much greater rates of prototropic rearrangement in the aprotic solvents compared with those in water. Further, examination of several reactions of N-(2-haloallyl)-ethanolamines with base in these solvents indicated that the reactions proceeded by initial dehydrohalogenation to the corresponding **2a**.



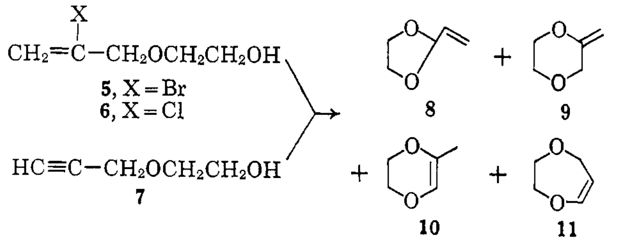
2a **3** **4**

In addition to methylenemorpholine formation and 2-vinyloxazolidine formation, two other cyclization reactions of N-alkyl-N-proparglyethanolmines and N-alkyl-N-(2-haloallyl)ethanolamines have been observed. Although substituted N-propargylethanolamines that contain no propargylic hydrogens undergo cyclization to 2-methylenemorpholines when treated with potassium hydroxide in boiling toluene or xylene,[4] a similar treatment of N-(2-hydroxyethyl)-N,4-dimethyl-4-amino-2-pentyne yields the seven-membered ring compound 4,5,5,7-tetramethyl-2,3,4,5-tetrahydro-1,4-oxazepine.[5] Also, the alkoxide of N-*t*-butyl-N-(2-chloroallyl)-1-amino-2-methyl-2-propanol in ether gives, in addition to the corresponding 2-vinyloxazolidine, a product tentatively identified as the isomeric 5,6-dihydro-1,4-oxazine.[3]

As a logical extension of our work with the N-(2-haloallyl)ethanolamines and N-propargylethanolamines, we directed our efforts to the study of base-induced cyclization reactions of the 2-haloallyloxyethanols **5** and **6** and proparglyoxyethanol (**7**). Early in this work, abstracts of two patents[6] appeared describing cyclization reactions of substituted propargyloxyethanols induced by potassium hydroxide. Interestingly, no mention was made in these patents of the identification as products of the corresponding 2-vinyl-1,3-dioxolanes or 3,6-dioxacycloheptenes.

Results

Treatment of the 2-haloallyloxyethanols **5** and **6** and propargyloxyethanol (**7**) with sodium hydroxide or potassium hydroxide was found to yield four cyclic products in varying amounts depending upon the conditions employed. These four products were found to be 2-vinyl-1,3-dioxolane (**8**), 2-methylene-1,4-dioxane (**9**), 2-methyl-1,4-dioxene (**10**), and 3,6-dioxacycloheptene (**11**).



5, X = Br
6, X = Cl
7
8 **9** **10** **11**

Identification of **8** was accomplished readily by comparison with material prepared from acrolein and ethylene glycol.[7] Tentative identification of **9** and **10**, which are also known compounds,[8] was made on the basis of their infrared and n.m.r. spectra. (The spectra of the cyclic ethers are described in detail in the Experimental section). Confirmation of the structures, however, proved to be less than straightforward because, when we attempted to prepare **9** by treatment of 2-iodomethyl-1,4-dioxane (**12**)[9] with sodamide in liquid

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[2] W. J. Croxall and J. H. Mellema, U. S. Patent 2,960,508 (Nov. 15, (1960); *Chem. Abstr.*, **55**, 14482 (1961).

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

[4] N. R. Easton, D. R. Cassady, and R. D. Dillard, *ibid.*, **28**, 448 (1963).

[5] N. R. Easton and R. D. Dillard, *Tetrahedron Letters*, 1807 (1963).

[6] (a) W. J. Croxall and N. D. Dawson, U. S. Patent 3,021,341 (Feb. 13, 1962); *Chem. Abstr.*, **57**, 11205 (1962). (b) W. J. Croxall and N. D. Dawson, U. S. Patent 3,048,598 (Aug. 7, 1962); *Chem. Abstr.*, **59**, 2828 (1963).

[7] R. F. Fischer and C. W. Smith, *J. Org. Chem.*, **25**, 319 (1960).

[8] R. K. Summerbell, G. H. Kalb, E. S. Graham, and A. L. Allred, *ibid.*, **27**, 4461 (1962).

[9] L. H. Werner and C. R. Scholz, *J. Am. Chem. Soc.*, **76**, 2701 (1954). The infrared and n.m.r. spectra of **12** are in accord with the assigned structure.

ammonia, only the dioxene **10** was obtained.[10] Identity of the **10** obtained from **12** was established by comparison of its physical properties with those reported for **10** and by virtue of its quantitative reaction with mercuric acetate. The structure of **9** was confirmed by its quantitative conversion to **10** over palladium on charcoal.[8] Tentative identification of **11** was also made on the basis of its infrared and n.m.r. spectra, and the structure was confirmed by reduction of **11** on Adams catalyst to a substance which had an elemental analysis, infrared spectrum, and n.m.r. spectrum completely consistent with those expected of 1,4-dioxepane.

Summarized in Table I are the yields and compositions of cyclic ethers **8**–**11** obtained from reactions of the hydroxyethyl ethers **5**–**7** with sodium hydroxide or potassium hydroxide in water, decalin, dimethyl sulfoxide, and triglyme.

TABLE I

YIELDS AND PRODUCT COMPOSITIONS OF CYCLIC ETHERS FROM REACTIONS OF HYDROXYETHYL ETHERS WITH SODIUM HYDROXIDE OR POTASSIUM HYDROXIDE[a]

Reactant	Solvent	Temp., °C.[b]	Yield, %[c]	Composition, %			
				8	**9**	**10**	**11**
5	Water	100	29	20	35	<2	45
7	Water	70	37	7	45	<2	48
7	Water	100	54	20	36	<2	44
5	Decalin	180	9	44	6	41	9
6	Decalin	180	17	52	4	40	4
7	Decalin	100	21	48	3	41	7
7	Decalin	180	23	47	2	45	6
5	DMSO	100	4	27	16	38	20
5	DMSO	150	7	27	7	58	9
6	DMSO	100	5	23	11	53	13
7	DMSO	70	25	19	6	65	10
7	DMSO	100	33	18	4	71	7
7	DMSO	150	31	20	3	70	6
5	Triglyme	180	7	51	<2	44	5
6	Triglyme	180	13	39	2	56	3
7	Triglyme	100	7	23	4	69	4
7	Triglyme	180	41	9	<2	83	8

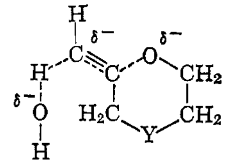
[a] Typical procedures are given in the Experimental section. [b] ±5°. [c] Not corrected for recovered starting material.

Discussion

Examination of the data in Table I shows that the course of cyclization reactions of the 2-haloallylethanols **5** and **6** and proparglyoxyethanol is strikingly dependent on the solvent used. In water, the seven-membered ring compound, 3,6-dioxacycloheptene (**11**), is the major product, and **11** and 2-methylene-1,4-dioxane (**9**) constitute 80% or more of the cyclic products formed. A significant amount of 2-vinyl-1,3-dioxolane (**8**) is also formed in water, but no 2-methyl-1,4-dioxene (**10**) was observed. In decalin, dimethyl sulfoxide, and triglyme, the major products are **8** and **10**. These compounds constitute 65–90% of the cyclic products formed in dimethyl sulfoxide, and more than 85% of the cyclic products formed in the other aprotic solvents. Of particular significance to interpreting how the cyclic products are formed are the observations that the relative amounts formed of both **8** and **10** appear to be independent of the relative amount formed of any other cyclic product, and that **9** and **11** are formed invariably in nearly equal amounts, **11** always predominating.

As treatment of an N-alkyl-N-(2-bromoallyl)ethanolamine (**1a**, X = Br, Y = NR, Z = O, n = 2) or an N-alkyl-N-propargylethanolamine (**2a**) with aqueous sodium hydroxide converts the compound to its corresponding 4-alkyl-2-methylenemorpholine (**3**), formation of 2-methylene-1,4-dioxane (**9**) on similar treatment of 2-bromoallyloxyethanol (**5**) and propargyloxyethanol (**7**) was expected. Quite unexpected was our finding that the major product from reactions in aqueous sodium hydroxide was the seven-membered ring compound, 3,6-dioxyacycloheptene (**11**). So far, no cyclization of a propargylaminoethanol to a seven-membered ring compound has been observed to occur in water. As 2-methylenemorpholine formation is known to occur by nucleophilic addition to acetylenic carbon, a similar mechanism for 2-methylene-1,4-dioxane formation seems probable. Further, as **9** and **11** are formed in approximately the same relative amounts under a wide range of reaction conditions, it seems likely that they arise from a common intermediate, specifically, the alkoxide of **7**. From these considerations, the most plausible mechanisms by which all or most of the **9** and **11** are formed are intramolecular nucleophilic additions of alkoxide to the internal and terminal acetylenic carbons, respectively, of **7**.

The formation of a substantial amount of **11** and **7** deserves additional comment. Assuming that 1% or more of a seven-membered ring product would have been detected together with the 2-methylenemorpholine formed by cyclization of a propargylaminoethanol in boiling aqueous sodium hydroxide, the difference in free energy of the transition states leading to the six- and seven-membered ring compounds from a propargylaminoethanol must be at least 3.4 kcal. It can be concluded, therefore, that substitution of –O– for >NR raises the energy of the transition state for six-membered ring formation (**12**) relative to that of the transition state for seven-membered ring formation (**13**) by more than 3.4 kcal. At least part of the >3.4-kcal. difference can be ascribed with certainty to electronic factors. In **13**, nitrogen or oxygen is one carbon removed and in **12** two carbons removed from the acetylenic carbon which becomes more negative at the transition state. Because oxygen is more electronegative than nitrogen, substitution of nitrogen by oxygen should result in stabilization of **13** relative to **12**. Less well defined is the contribution of steric factors to the course of cyclization reactions of propargylaminoethanols and propargyloxyethanol (**7**). Because of the subtle differences in geometry arising from substitution of oxygen for nitrogen and the differences in nonbonded interactions that result, a 2-methylenemorpholine may be considerably more stable relative to its seven-membered ring isomer than is **9** relative to **11**. As a difference in the stabilities of the six- and seven-mem-



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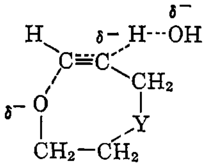

13

Y = NR or O

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[10] This preparation has previously been observed to give variable results.[8]

bered ring products can be expected to be reflected to a degree in their respective transition states, steric factors may well be the major cause of the dramatic difference in behavior of propargylaminoethanols, and propargyloxyethanol (**7**) in aqueous sodium hydroxide solution.

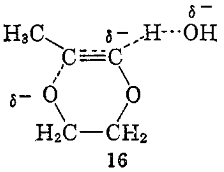
A more easily explainable difference in the behavior in water of an N-propargylethanolamine and propargyloxyethanol (**7**) is the observed conversion of the latter to a five-membered ring compound, 2-vinyl-1,3-dioxolane (**8**). The analogous five-membered ring product from an N-alkyl-N-propargylethanolamine, the 2-vinyloxazolidine (**4**), is unstable in water.

Although the major and oftentimes sole product obtained from the reaction of an N-propargylethanolamine or an N-(2-haloallyl)ethanolamine with potassium hydroxide or sodium hydroxide in dimethyl sulfoxide, ether, or toluene is the corresponding **4**, reactions of the hydroxyethyl ethers **5–7** with the same bases in the same or similar aprotic solvents failed to give 2-vinyl-1,3-dioxolane (**8**) as the sole product. Indeed, only with decalin as the solvent was **8** consistently observed to be the major product; in dimethyl sulfoxide and in triglyme (for **6** and **7**), the major product is 2-methyl-1,4-dioxene (**10**).

The only plausible mechanism that can account for formation of **8** is intramolecular nucleophilic addition of alkoxide to the internal allenic carbon of allenyloxyethanol (**14**), which can be formed by base-induced prototropic rearrangement of **5**. Comparison of the mechanism for 2-vinyldioxolane formation with the similar mechanism proposed for 2-vinyloxazolidine formation[3] is helpful in rationalizing the different behavior in aprotic solvents of the hydroxyethyl ethers **5–7** and their amine analogs. Consider first the role of the heteroatom in polarizing the C-1–C-2 bond of the allene moiety by resonance, *i.e.*, $C{=}C{=}C{-}Y \longleftrightarrow C{=}\bar{C}{-}C{=}\overset{+}{Y} \longleftrightarrow C{=}\bar{C}{-}\overset{+}{C}{-}Y$. Because oxygen is more electronegative than nitrogen, the polar resonance forms are expected to be less important for allenyl ethers than allenylamines. If the transition state for five-membered ring formation retains to a degree the polarization of the allene C-1–C-2 bond, ring closure of the allenylamine to the 2-vinyloxazolidine will be a more rapid reaction than ring closure of **14** to **8**. Another factor that must be considered is the effect of the heteroatom on the rate of prototropic rearrangement. As prototropic rearrangement of a propargyl group to an allenyl group occurs *via* a carbanion intermediate that is formed by rate-determining abstraction of a proton from propargyl carbon, prototropic rearrangement should occur less rapidly for a propargylamine than for **7**, which contains the better electron-withdrawing atom at propargyl carbon. For the same reasons, continued rearrangement of the allenyl ether **14** to the 1-propynyl ether **15** should occur more rapidly than rearrangement of the allenylamine to the 1-propynylamine. Summarizing, we conclude that the decreased relative importance of the five-membered ring product that comes about on substitution of -O- for >NR is the result of an increased rate of prototropic rearrangement and a decreased rate of cyclization of the intermediate allene.

$H_2C{=}C{=}CHOCH_2CH_2OH$ **14** $H_3CC{\equiv}C{-}OCH_2CH_2OH$ **15**

Most or all of the 2-methyl-1,4-dioxene **10** must be formed by cyclization of the 1-propynyl ether **15**, presumably *via* a transition state that can be represented by **16**. Control experiments showed that the cyclic products **8–11** are stable under the reaction conditions in dimethyl sulfoxide, and these experiments justify the conclusion that none of the **10** is formed in dimethyl sulfoxide by prototropic rearrangement of 2-methylene-1,4-dioxane (**9**). Satisfactory controls were not possible in decalin and triglyme, but the similar and low yields of **9** and **11** indicate that little if any **10** arises from **9** in these solvents. It is possible that some **10** (or **9** or **11**) is formed together with **8** from allenyloxyethanol (**14**), but the wide variation in the observed **8**:**10** ratios, >10 in water, <0.11 in triglyme at 180°, indicates that little if any **10** is formed by cyclization of **14**.



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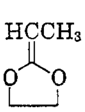
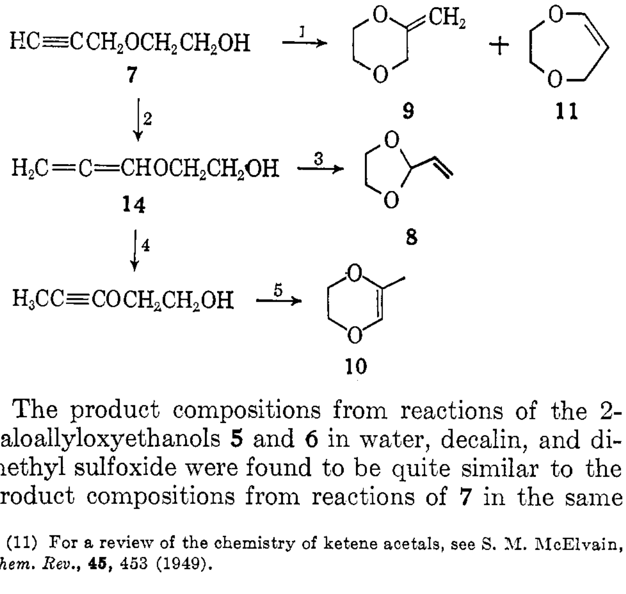


17

Our results do not preclude the possibility that considerable 2-propylidine-1,3-dioxolane (**17**) is also formed from **15** in the aprotic solvents, and that **17** escapes detection because it is unstable under the reaction conditions.[11]

Our explanations of the reactions with base of propargyloxyethanol (**7**) can be summarized with the aid of the accompanying reaction sequence. In water, the principal reaction is 1, cyclization of the alkoxide of **7** to give 2-methylene-1,4-dioxane (**9**) and 3,6-dioxacycloheptene (**11**) in nearly equal amounts. Competing with 1 is 2, prototropic rearrangement of **7** to allenyloxyethanol (**14**), which, in water, undergoes reaction 3, cyclization to 2-vinyl-1,3-dioxolane (**8**), considerably more rapidly than reaction 4, prototropic rearrangement to the 1-propynyl ether **15**. In the aprotic solvents, the rates of the prototropic rearrangements 2 and 4 are enhanced relative to the rates of their competing ring-closure reactions 1 and 3, and the major products become **8**, formed from 3, and 2-methyl-1,4-dioxene (**10**), formed from 5, cyclization of **15**.



The product compositions from reactions of the 2-haloallyloxyethanols **5** and **6** in water, decalin, and dimethyl sulfoxide were found to be quite similar to the product compositions from reactions of **7** in the same

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[11] For a review of the chemistry of ketene acetals, see S. M. McElvain, *Chem. Rev.*, **45**, 453 (1949).

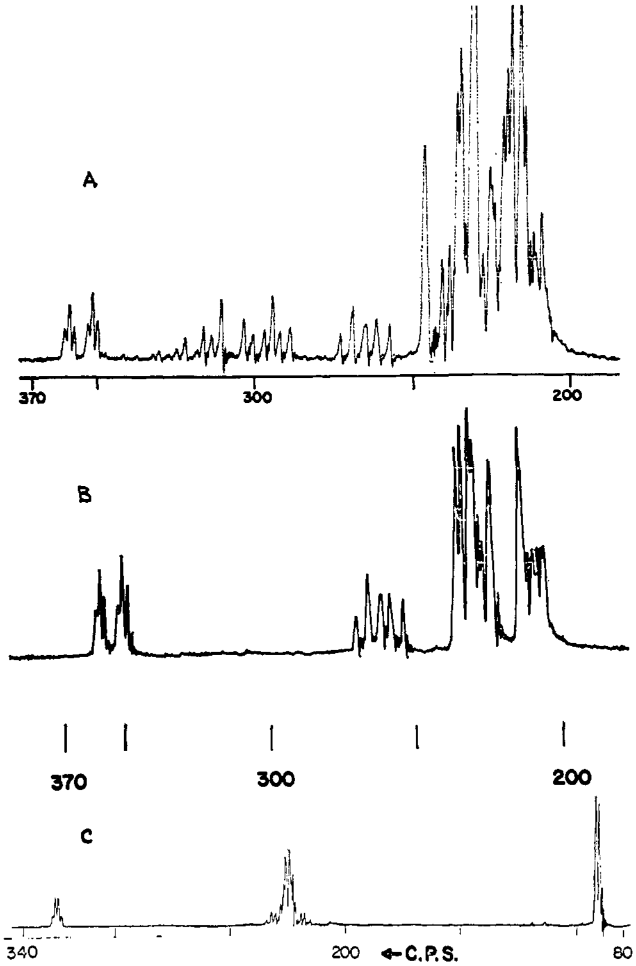

Figure 1.—N.m.r. spectra at 56.4 Mc. of (A) a mixture of cyclic ethers obtained from propargyloxyethanol (**7**) and 2 *N* sodium hydroxide at 100°; (B) 3,6-dioxyacycloheptene (**11**); and (C) 2-methyl-1,4-dioxene (**10**). Clearly discernible in A are (1) bands due to 2-vinyl-1,3-dioxolane (**8**) at 342–288 c.p.s., (2) bands due to **11** centered at 351 and 358 c.p.s. and at 270–254 c.p.s., and (3) the intense band due to 2-methylene-1,4-dioxane (**10**) at 245 c.p.s. Spectra were taken of neat liquids.

solvent. From this, we conclude that the principal reaction of **5** or **6** in these media is dehydrohalogenation to **7** rather than prototropic rearrangement to a 2-halopropenyl ether or dehydrohalogenation to **14**. A similar conclusion also seems warranted concerning the reactions in triglyme. If the 2-haloallyloxyethanol had undergone elimination to **14** or prototropic rearrangement to a 2-halopropenyl ether (followed by elimination to **14** or **15**), this would be expected to lead to a larger percentage of **10** in the product rather than to what was actually observed, *i.e.*, a larger percentage of **8**. The differences observed are probably due to a difference in medium that is the result of the water formed in reactions of **5** and **6** with potassium hydroxide.

Compared with the previous study of base-induced cyclization reactions of N-(2-haloallyl)ethanolamines (**1a**) and N-propargylethanolamines (**2a**),[3] our study of base-induced cyclization reactions of the hydroxyethyl ethers **5–7** proved to be even more informative regarding the scope and mechanisms of reactions of 2-haloallyl and propargyl compounds. We now know that the direction of ring closure followed by a propargyl compound is determined not only by the nature of the reaction medium but also by a delicate balance of electronic and steric factors.

Experimental

Boiling points are uncorrected. Infrared spectra were obtained with a Beckman IR-4 spectrophotometer. N.m.r. spectra were determined at 56.4 Mc. with a Varian Associates HR-60 system equipped with electronic integrator and base-line stabilizer. Resonance frequencies in n.m.r. 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 (g.l.p.) chromatograms 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.

2-Hydroxyethyl Ethers 5–7.—The following procedure is typical. To a rapidly stirred solution prepared by adding 23 g. (1.0 mole) of sodium in 4 hr. to 660 ml. of ethylene glycol was added 200 g. (1.0 mole) of 2,3-dibromopropene in 2.5 hr. When the addition was complete, the reaction mixture, which had been maintained at 30–40°, was heated to 70–80° for 1.5 hr. The reaction mixture was cooled and added to 500 ml. of water and 400 ml. of ether. The phases were separated, and the aqueous phase was extracted four times with 150-ml. portions of ether. The ether extracts were combined, dried with potassium carbonate, and distilled. **2-(2-Bromoallyloxy)ethanol** (**5**, 120 g., 66%) was collected at 88–90° (8 mm.), $n^{25}\mathrm{D}$ 1.4872. The n.m.r. spectrum at 30° of **5** containing ~2% TMS consists of bands centered at 349 and 331 c.p.s. ($CH_2=$), a singlet at 273 c.p.s. (OH), a band centered at 252 c.p.s. ($=C-CH_2$), and a multiplet at 238–214 c.p.s. (OCH_2CH_2O).

Anal. Calcd. for $C_5H_9BrO_2$: C, 33.18; H, 5.02; Br, 44.12. Found: C, 33.42; H, 5.10; Br, 43.89.

2-(2-Chloroallyloxy)ethanol (**6**), b.p. 81–82° (9 mm.), $n^{24}\mathrm{D}$ 1.4600, was obtained in 76% yield from 111 g. (1.0 mole) of 2,3-dichloropropene and 660 ml. of ethylene glycol in which had been dissolved 23 g. (1.0 mole) of sodium. The n.m.r. spectrum at 30° of **6** containing ~2% TMS consists of bands centered at 328 and 317 c.p.s. ($CH_2=$), a singlet at 279 c.p.s. (OH), a band centered at 245 c.p.s. ($=C-CH_2$), and a multiplet at 231–211 c.p.s. The band at lowest field at 56.4 Mc. is an apparent quartet, $J_{ap} \sim 1.5$ c.p.s.

Anal. Calcd. for $C_5H_9ClO_2$: C, 44.00; H, 6.64; Cl, 25.98. Found: C, 43.87; H, 6.84; Cl, 25.78.

Propargyloxyethanol (**7**) was obtained in 32% yield from 75 g. (1.0 mole) of propargyl chloride and 660 ml. of ethylene glycol in which had been dissolved 23 g. (1.0 mole) of sodium. The product had b.p. 70–73° (9 mm.), $n^{22}\mathrm{D}$ 1.4491 [lit.[6] b.p. 75–80 (12–14 mm.), $n^{25}\mathrm{D}$ 1.4508]. The n.m.r. spectrum at 30° of **7** containing ~2% TMS consists of a doublet, $J \sim 2.1$ c.p.s., at 230 c.p.s. ($C\equiv C-CH_2$), a singlet at 223 c.p.s. (OH), a multiplet at 205–195 c.p.s. (OCH_2CH_2O), and a triplet, $J \sim 2.1$ c.p.s., at 147 c.p.s. ($HC\equiv$).

Preparation and Identification of the Cyclic Ethers 8–11.—A solution of 60 g. (0.60 mole) of **7** and 600 ml. of 2 *N* sodium hydroxide was heated under reflux for 12 hr. The reaction mixture was cooled and the two-phase mixture was extracted four times with 100-ml. portions of ether. The ether extracts were combined and distilled to yield 39 g. (65%) of clear, colorless product with b.p. 59–63° (80 mm.). The infrared spectrum of the product possessed an intense band at 1660 cm.$^{-1}$, which indicated the presence of a polar carbon–carbon double bond, a band of moderate intensity at 1630 cm.$^{-1}$, which indicated the presence of another double bond, and no band in the 3300-cm.$^{-1}$ region, which indicated the absence of an O–H bond. The n.m.r. spectrum, shown as Figure 1A, consisted of a large number of bands at 365–205 c.p.s. Analysis by g.l.p. chromatography on a 0.25 in. × 10 ft. column packed with nonyl phthalate on firebrick indicated that the product consisted of three components. The minor component, b.p. 114–115°, which constituted about 20% of the mixture, was identified as **2-vinyl-1,3-dioxolane** (**8**) by comparison of its n.m.r. spectrum and retention times on three g.l.p. chromatography columns with those of **8** prepared from acrolein and ethylene glycol.[7] The n.m.r. spectrum of **8** consists of numerous lines from 364 to 287 c.p.s. [$CH_2=CH-C(H)<$] and a multiplet from 225 to 209 c.p.s. (OCH_2CH_2O) (*cf.* Figure 1A). The other components, present in nearly equal amounts, condistilled at 123–124° and could not be separated by distillation through a 13 mm. × 1.2 m. Nester spinning-band still.[12] Separation was achieved by preparative-scale g.l.p. chromatography on the nonyl phthalate column. The n.m.r. spectrum of the major component subsequently identified as **2-methylene-1,4-dioxane** (**10**) consisted of intense bands at 245 (CH_2=?), 231 (C=C—CH_2?), and 228 c.p.s. (OCH_2CH_2O). The other major component, identified as **3,6-dioxacycloheptene** (**11**), had n^{22}D 1.4574 and an n.m.r. spectrum (Figure 1B) that consisted of a doublet, $J \sim 7.3$ c.p.s., centered at 355 c.p.s. (=CH—O), each component of which was split into a triplet ($J \sim 1.5$ c.p.s.), a multiplet centered at 262 c.p.s. (=CH—C) with an average separation of ~3.9 c.p.s. between the five major lines, a discernible doublet ($J \sim 3.9$ c.p.s.) centered at 235 c.p.s. (=C—CH_2O), each component of which was split into a doublet ($J \sim 1.5$ c.p.s.), and a multiplet from ~235 to 206 c.p.s. (OCH_2CH_2O) with no significant component from 223 to 213 c.p.s.

Anal. Calcd. for $C_5H_8O_2$: C, 59.98; H, 8.05. Found: C, 59.52; H, 7.74.

Compound **11** (2.1 g., 21 mmoles) in 20 ml. of freshly distilled cyclohexane was hydrogenated over Adams catalyst for 2 hr. at 22–27 p.s.i.g. The catalyst was removed by filtration, and the residue was concentrated by distillation through the spinning-band column. Continued distillation gave 1.4 g. (65%) of 1,4-dioxepane, b.p. 106–107°, n^{25}D 1.4313. The n.m.r. spectrum consisted of an apparent triplet ($J_{ap} \sim 5.9$ c.p.s.) centered at 217 c.p.s. (OCH_2-C-CH_2O), a singlet a 211 c.p.s. (OCH_2CH_2O), and an apparent quintet ($J_{ap} \sim 5.9$ c.p.s.) centered at 111 c.p.s. (CCH_2C).

Anal. Calcd. for $C_5H_{10}O_2$: C, 58.79; H, 9.87. Found: C, 58.72; H, 10.02.

In an attempt to prepare **9**, 45 g. (0.20 mole) of iodomethyl-1,4-dioxane[9] was treated with 7.8 g. (0.20 mole) of sodamide as described by Summerbell, *et al.*[8] The product (8.7 g., 43%) had b.p. 112–114°, n^{23}D 1.4398 (lit.[8] b.p. 112°, n^{25}D 1.4477 for **9**). The infrared spectrum possessed an intense band at 1690 cm.$^{-1}$ which is also characteristic of **10**. The n.m.r. spectrum (Figure 1C) of the product consisted of a quartet ($J \sim 1.2$ c.p.s.) centered at 326 c.p.s., a multiplet from 236 to 215 c.p.s., and a doublet ($J \sim 1.2$ c.p.s.) centered at 91 c.p.s., which are assigned, respectively, to the vinyl, methylene, and methyl hydrogens of **10**. The n.m.r. spectrum is incompatible with the **2-methylene-1,4-dioxane** (**9**) structure. That the product was indeed **2-methyl-1,4-dioxene** (**10**) was confirmed by observing its reaction with mercuric acetate,[8] which gave mercury in 94% yield.

The availability of pure **10** made possible confirmation of the structure of **9**, which was accomplished through its quantitative conversion to **10** using the procedure of Summerbell, *et al.*[8] A mixture (4.2 g.) of **9** (45%) and **11** (55%), 4.2 g. of biphenyl, 0.8 g. of hydroquinone, and 0.46 g. of 5% palladium on charcoal was heated under reflux in a nitrogen atmosphere for 24 hr. Distillation yielded 3.0 g. of a mixture that was 60% **10** and 40% **11** as indicated by g.l.p. chromatography and confirmed by n.m.r. spectroscopy.

A slurry prepared from 6 g. (0.15 mole) of coarsely powdered sodium hydroxide and 150 ml. of redistilled dimethyl sulfoxide was stirred vigorously and heated to 100°. Propargyloxyethanol (**7**, 30 g., 0.30 mole) was added in 10 min., the reaction mixture was heated with stirring for an additional 40 min., cooled, and added to 150 ml. of water. The aqueous solution was extracted three times with 60-ml. portions of ether, and the ether extracts were combined and distilled to yield 11.8 g. (39%) of clear, colorless product with b.p. 113–123°. Analysis by g.l.p. chromatography indicated that the product consisted mostly of **2-methyl-1,4-dioxene** (**10**) together with small amounts of **8**, **9**, and **11**, and this indication was confirmed by examination of the infrared and n.m.r. spectra of the product.

G.l.p. Chromatography of the Cyclic Ethers 8–11.—Analysis of mixtures of the cyclic ethers was routinely carried out using at least two different gas chromatography columns. The most satisfactory columns were a 0.25 in. × 10 ft. column packed with nonyl phthalate on firebrick and a 0.25 in. × 15 ft. column packed with Cyanosilicon XF-1150 on W-HMDS. Using the former column at 108° with a helium flow rate of 60 cc./min. gave retention times of 15.6, 22.5, 16.9, and 25.6 min. for **8**, **9**, **10**, and **11**, respectively; using the latter column at 112° with a helium flow rate of 80 cc./min. gave retention times of 10.4, 13.7, 9.4, and 12.8 min. for **8**, **9**, **10**, and **11**, respectively. A 0.25 in. × 15 ft. column packed with Carbowax 20M (alkaline) at 127° with a helium flow rate of 80 cc./min. gave retention times of 11.3, 16.3, 11.6, and 11.6 min. for **8**, **9**, **10**, and **11**, respectively.

In all analyses, the relative mole fraction of each cyclic ether was taken as equal to its relative peak height in gas chromatograms obtained using the column packed with Cyanosilicon XF-1150 or Carbowax 20M (alkaline). Specifically, the mole fraction of **8** in a typical mixture was taken as equal to the peak height of the elution band due to **8** divided by the sum of the peak heights of the elution bands due to all the cyclic ethers. This relationship was tested and found to be valid to ±2% with known mixtures of **8**, **9**, and **11**, and of **9**, **10**, and **11**, on the column packed with Cyanosilicon XF-1150.

Reactions of the Hydroxyethyl Ethers 5, 6, and 7 with Sodium Hydroxide or Potassium Hydroxide. A. In Water.—The following is a typical procedure. To 100 ml. of boiling, vigorously stirred 2 *N* sodium hydroxide was added 18.1 g. (0.10 mole) of 2-(2-bromoallyloxy)ethanol (**5**). Heating and stirring were continued for 12 hr. The mixture was cooled and extracted four times with 15-ml. portions of ether. The ether extracts were combined, dried with magnesium sulfate, concentrated to 30 ml. by distillation, and analyzed by g.l.p. chromatography using the Carbowax 20M (alkaline) column. The ether solution was distilled through a semimicro Vigreux column, and the 1.9-g. (19%) fraction with b.p. 56–66° (80 mm.) was collected and analyzed on the Cyanosilicon XF-1150 column. The analytical results are summarized in Table I. The infrared and n.m.r. spectra and the analysis obtained using the Carbowax 20M (alkaline) column were found to be consistent with the analysis obtained using the Cyanosilicon column.

B. In Dimethyl Sulfoxide.—The following is typical. A vigorously stirred slurry prepared from 6 g. (0.15 mole) of coarsely powdered sodium hydroxide and 100 ml. of dimethyl sulfoxide was heated to and held at 150° with an oil bath, and 18.1 g. (0.10 mole) of **5** was added rapidly (<2 min.). Heating and stirring were continued for 15 min. The reaction mixture was cooled and added to 100 ml. of water, and the aqueous solution was extracted three times with 20-ml. portions of ether. The ether extracts were combined and worked up as described for the ether extracts obtained from reactions in water. The yield and product analysis are given in Table I. For reactions of propargyloxyethanol, 0.5 equiv. of sodium hydroxide/mole was used rather than 1.5 equiv. Reaction times at 70 and 100° were 90 and 45 min., respectively.

C. In Decalin and Triglyme.—The following is typical. A slurry prepared from 4.2 g. (0.075 mole) of coarsely powdered potassium hydroxide and 75 ml. of redistilled decalin and contained in a 100-ml. flask equipped with stirrer, dropping funnel, and distillation head, was stirred vigorously and heated to 180 ± 5° in an oil bath. Propargyloxyethanol (**7**, 15 g., 0.15 mole) was added dropwise in 15 min. During the addition, the volatile product distilled from the reaction mixture. When distillation slowed, the temperature of the oil bath was raised to 195° and held at that temperature for 10 min. The distillate was analyzed using the Carbowax 20M (alkaline) column and then redistilled. The fraction with b.p. 55–65° (80 mm.) was collected and analyzed using the Cyanosilicon column. Summarized in Table I are the yield and the analysis. The latter was compatible with the infrared spectrum of the product and the analysis of the crude product obtained using the Carbowax 20M (alkaline) column.

Each reaction with **7** at 100° was carried out for 12 hr. The reaction mixture was filtered, and the product was isolated by distillation.

Reactions of the 2-haloallyloxyethanols **5** and **6** were carried out using 1.5 equiv. of potassium hydroxide/mole of alcohol. Water formed during each of these reactions and codistilled with the product. The distillate was extracted with 30 ml. of ether, the phases were separated, the organic phase was dried, and the product was isolated by distillation.

Stability of the Cyclic Ethers.—A vigorously stirred slurry prepared from 0.7 g. (0.017 mole) of coarsely powdered sodium hydroxide, 2.1 g. (0.021 mole) of a mixture composed of 5% **8**, 40% **9**, 5% **10**, and 50% **11**, and 15 ml. of dimethyl sulfoxide was heated to and held at 120° for 1 hr. The mixture was added to 15 ml. of water, and the aqueous solution was extracted three

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(12) R. G. Nester, *Anal. Chem.*, **28**, 278 (1956). The still was obtained from Nester/Faust, Newark, Del.

times with 10-ml. portions of ether. The ether extracts were combined, dried with magnesium sulfate, and concentrated to a volume of 4 ml. by distillation. Analysis by g.l.p. chromatography indicated that the composition of the mixture of cyclic ethers was unchanged.

2-Vinyl-1,3-dioxolane (**8**, 5 g., 0.05 mole) was treated in the same manner with 1.6 g. (0.04 mole) of sodium hydroxide in 40 ml. of dimethyl sulfoxide at 120°. The recovered **8** weighed 4.2 g. (84%), and examination of its infrared spectrum and g.l.p. chromatograms indicated that it was free of impurities.

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cis- and *trans*-3-Alkyl-2-methyloxiranes and 3-Alkyl-1,2-dimethylaziridines[1a-c]

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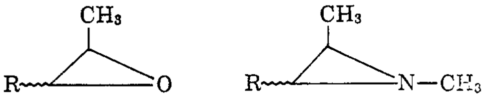
Syntheses are reported of a series of *cis*- and *trans*-3-alkyl-2-methyloxiranes (**1a–h**) and the corresponding *cis*- and *trans*-3-alkyl-1,2-dimethylaziridines (**2a–h**). The stereospecificity of conversion of sulfate esters of amino alcohols to aziridines is discussed briefly. The *cis*-oxiranes were found to have higher boiling points, refractive indices, and densities than their *trans* isomers, but the *cis*-aziridines were found to have the lower of these physical properties. The structural assignments to the 3-*n*-propyl-2-methyloxiranes are corrected, and the applicability of current versions of the von Auwers–Skita rule to aziridines, oxiranes, and other heterocyclic compounds is discussed.

A recent statement[2] of the von Auwers–Skita rule relating physical properties to isomer structure is "with cyclic stereoisomers in which the substituents are bound to configurationally identical ring systems, the isomer with the higher density and the higher refractive index is that which has the higher heat content."[3] Usually, the (higher) boiling point and (lower) molar refraction can be related in a similar manner. Interestingly, there appears to be no previous examination of the applicability of this or similar rules[2,4] to small-ring heterocyclic systems.

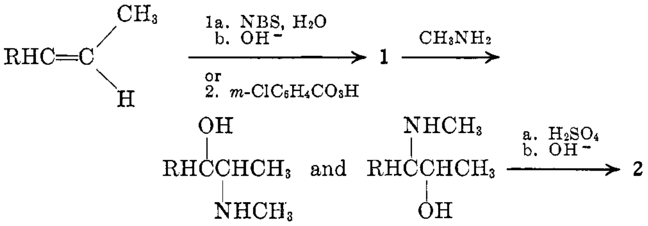
As a preliminary to the study of certain aspects of the relationship of structure to reactivity of aziridines and aziridinium compounds, we prepared several pairs of *cis*- and *trans*-3-alkyl-1,2-dimethylaziridines (**2a–h**). These syntheses required preparation of the corresponding *cis*- and *trans*-3-alkyl-2-methyloxiranes (**1a–h**), which served as intermediates in the preparations of the aziridines. This work therefore made available a sufficient number of compounds for evaluation of the applicability of current versions of the von Auwers–Skita rule to small-ring heterocyclic systems. We report here the syntheses of the aziridines **2a–h** and the oxiranes **1a–h** together with their relevant physical properties.



1a, R = *cis*-CH_3
b, R = *trans*-CH_3
c, R = *cis*-C_2H_5
d, R = *trans*-C_2H_5

2e, R = *cis*-*i*-C_3H_7
f, R = *trans*-*i*-C_3H_7
g, R = *cis*-*t*-C_4H_9
h, R = *trans*-*t*-C_4H_9

The procedures used for syntheses of **1a–h** and **2a–h** are outlined in the accompanying reaction sequence.



Although details have been given for the preparation of *trans*-3-isopropyl-1,2-dimethylaziridine (**2f**) by the first procedure,[5] some discussion of the preparation of the aziridines is desirable because structural variation required marked changes in conditions in some cases and caused notable differences in results in others.

Commercial alkene with N-bromosuccinimide and water was transformed to its bromohydrin or bromohydrins, and this product was converted with aqueous base to the corresponding oxirane (**1**). As for preparations of *cis*- and *trans*-3-isopropyl-2-methyloxirane (**1e** and **1f**), the two-step procedure gave over-all yields of **1a–d** of better than 70%; however, yields of *cis*- and *trans*-3-*t*-butyl-2-methyloxirane (**1g** and **1h**, respectively) were less than 30%.[6] Fortunately, the use of *m*-chloroperbenzoic acid made possible preparation of **1g** and **1h** from the corresponding alkene in yields of better than 65%. Conversions of the alkenes to the oxiranes by both methods were highly stereo-

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[1] (a) Structure–Activity Relationships of Ethylenimines. V. (b) Previous paper in the series: A. T. Bottini and R. L. VanEtten, *J. Org. Chem.*, **30**, 575 (1965). (c) This research was supported by Grant CA-05528 from the National Cancer Institute of the Public Health Service. (d) Public Health Service Predoctoral Fellow, 1963–1964.

[2] H. Van Bekkum, A. Van Veen, P. E. Verkade, and B. M. Wepster, *Rec. trav. chim.*, **80**, 1310 (1961). Earlier statements of the von Auwers-Skita rule are discussed in this reference.

[3] (a) The significance of relating the von Auwers–Skita rule to enthalpy rather than free energy had been discussed earlier.[3b] (b) N. L. Allinger, *J. Am. Chem. Soc.*, **79**, 3443 (1957).

[4] (a) Although olefins appear to follow the dipole rule (van Arkel rule), according to which the isomer of higher dipole moment has the higher physical constants regardless of enthalpy (see ref. 3b and references cited therein), it is not yet clear when saturated cyclic stereoisomers can be expected to follow the dipole rule.[2,4b] Conceivably, saturated cyclic stereoisomers with appreciably different dipole moments may follow the dipole rule rather than the quoted version or similar versions of the von Auwers–Skita rule.[4c] (b) N. L. Allinger and R. J. Curby, Jr., *J. Org. Chem.*, **26**, 933 (1961). (c) *Cf.* E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, pp. 216, 217.

[5] A. T. Bottini, R. L. VanEtten, and A. J. Davidson, *J. Am. Chem. Soc.*, **87**, 755 (1965).

[6] A rationale for the poorer yields of **1g** and **1h** is that conversion of a *t*-butylethylene to a bromohydrin is more likely to be accompanied by carbonium ion rearrangement than is similar conversion of a primary or secondary alkylethylene. *Cf.* the study of the addition of hydrogen chloride to *t*-butylethylene reported by G. G. Ecke, N. C. Cooke, and F. C. Whitmore [*ibid.*, **72**, 1511 (1950)].