A Ring-Expansion Reaction. The Rearrangement of 1-Isopropenylcycloalkanol Epoxides

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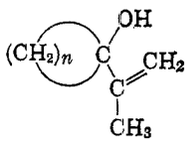
A series of 1-isopropenylcycloalkanol epoxides has been prepared and rearranged by catalysis with boron trifluoride etherate or acidic alumina to the ring-enlarged 2-methyl-2-hydroxymethylcycloalkanones.

Recently it has been demonstrated that the reaction of 1-isopropenylcycloalkanols (**1**) with *t*-butyl hypochlorite produces the ring-enlarged 2-chloromethyl-2-methylcycloalkanones **2**.[2] This reaction was envi-



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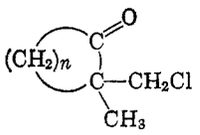

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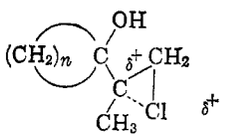
sioned as proceeding through the cyclic chloronium ion (**3**) with significant localization at cationic character



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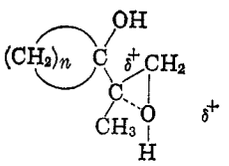

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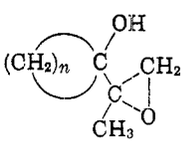
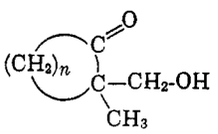
on the tertiary carbon atom. The similarity between **3** and the corresponding protonated epoxy alcohol (**4**) is immediately apparent. The preparation and some acid-catalyzed rearrangements of the epoxy alcohols **5–7** are the subjects of this report.



5, $n=3$
6, $n=4$
7, $n=5$



8, $n=3$
9, $n=4$
10, $n=5$

The epoxy alcohols **5–7** were obtained in good yields from the previously prepared olefins[2,3] by oxidation with *m*-chloroperbenzoic acid in chloroform solution. The lack of direct rearrangement of the olefins to keto alcohols **8–10** during the oxidation with per acid is undoubtedly an indication that little cationic charge resides on the tertiary carbon (as in **4**) during the epoxidation process.

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(2) C. R. Johnson, C. J. Cheer, and D. J. Goldsmith, *J. Org. Chem.*, **29**, 3320 (1964).

(3) An improved method of preparation of these allylic alcohols will be described in a forthcoming publication.

(4) For interesting commentaries on the mechanism of per acid epoxidation of olefins, the reader is referred to K. D. Binghan, G. D. Meakins, and G. H. Whitman, *Chem. Commun.*, 445 (1966), and H. Kwart and D. M. Hofmann, *J. Org. Chem.*, **31**, 419 (1966), and references cited therein.

The nmr spectra of the homologous epoxy alcohols all show a three-proton singlet at δ 1.29–1.30 and ring protons as complex multiplets at 1.95, 1.60, and 1.55 for **5**, **6**, **7**, respectively. All three compounds exhibit the oxirane methylene protons as a typical AB quartet between δ 2.3 and 2.9 with $J = 5$ cps. The low-field doublet also exhibits further fine splitting, $J = ca.$ 1 cps.

Attempts to effect the conversion of epoxy alcohol **6** into ring-expanded keto alcohol **9** by treatment with boron trifluoride etherate in benzene, ether, or hexane were dissappointing from the point of view of synthetic utility. When chloroform or methylene chloride were employed as solvents the rearrangement of **6** to **9** proceeded in reasonable yield. The four- and six-membered analogs (**5** and **7**, respectively) demonstrated that the reaction was expectedly a function of ring size,[2,5,6] as indicated in Table I. No attempts were made to identify other products formed from the reaction of epoxy alcohols **5–7**.

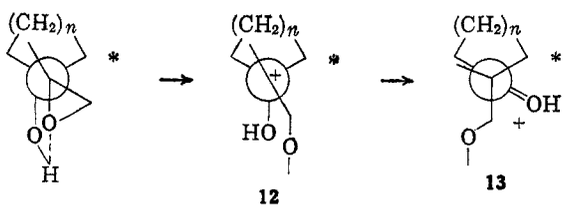
TABLE I

REACTION WITH BORON TRIFLUORIDE ETHERATE

Epoxy alcohol	Solvent	Yield, %[a] (ketone)
6	C_6H_6[b]	29 (9)
6	Et_2O[c]	14 (9)
6	Hexane[c]	14 (9)
5	CH_2Cl_2[d]	63 (8)
6	CH_2Cl_2[d]	49 (9)
7	CH_2Cl_2[d]	15 (10)

[a] Estimated by gas chromatography. [b] 0.1 equiv of $BF_3 \cdot Et_2O$, 0°, 5 min. [c] 1.0 equiv of $BF_3 \cdot Et_2O$, 25°, 1 hr. [d] 0.33 equiv of $BF_3 \cdot Et_2O$, −5°, 2–4 min.

An examination of Dreiding models of the starting epoxy alcohols indicated that, in hydrogen-bonded conformer **11**, one of the ring carbon atoms (denoted by an asterisk) is held in a position suitably situated to migrate to the positive terminus generated by opening of the epoxide ring (**11** → **13**). It was this rationale which



11 **12** **13**

(5) B. Tchoubar, *Bull. Soc. Chim. France*, 164 (1949).

(6) R. A. Raphael in "The Chemistry of Carbon Compounds," Vol. IIA, E. Rodd, Ed., Elsevier Publishing Co., New York, N. Y., 1953, p 11.

led to the speculation that a heterogeneous catalyst might be more effective in promoting the desired ring-expansion reaction, provided that both oxygen atoms of the epoxy alcohol were involved in adsorption on the catalyst surface. This, in effect, would constrain the molecule in the desired conformation **11**. Acidic alumina has been demonstrated to be an efficient catalyst in the rearrangements of α,β-epoxy ketones[7] and 17β-hydroxy-20-keto steroids.[8] It has also been utilized in the stereospecific dehydration of bornyl and isobornyl alcohols.[9]

Treatment of epoxy alcohol **7** with acidic alumina in benzene at room temperature produced only recovered starting material. However, refluxing the reaction mixture overnight effected the desired rearrangement to keto alcohol **10** in 49% yield. The conversion of epoxy alcohol **6** to keto alcohol **9** is effected in only 2 hr, but the yield is not significantly improved over the boron trifluoride catalyzed reaction in methylene chloride. Longer reaction times cause a decrease in yield (Table II).

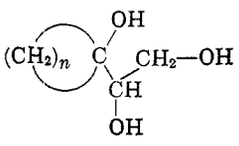
TABLE II

REACTION WITH ACIDIC ALUMINA[a]

Epoxy alcohol	Time, hr	Yield, % (ketone)
6	2	52 (**9**)
6	12	26 (**9**)
7	12	49 (**10**)

[a] One gram of alumina per millimole of epoxy alcohol in 20 ml of dry benzene.

The major impurities in the alumina reactions of epoxy alcohols **6** and **7** are viscous oils, which tenaciously cling to the catalyst and are removed only by wet methanol. The infrared spectra of these oils exhibit intense absorption in the hydroxyl stretching region. We have tentatively assigned to these compounds the triol structure **14**, which could reasonably



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arise *via* hydrolysis of the epoxides on the alumina surface, but they have not been investigated further. A shortage of material prevented the study of the alumina-catalyzed ring expansion of the cyclobutanol system (**5**).

The proposed mechanism for the alumina-catalyzed rearrangement of the epoxy alcohols (*viz.* **11** → **13**), poses interesting stereochemical questions in the case where the carbocyclic ring is unsymmetrically substituted. A surface reaction involving both oxygen atoms places rigid stereochemical restrictions on the reacting epoxy alcohols. Unsymmetrical substitution of the carbocyclic ring allows the epoxy alcohols to exist as diastereomeric pairs, the structures of which will dictate the stereochemical outcome of the rearrangement. This question is being currently studied and will be the subject of a future report.

(7) H. Hoffmann, *Angew. Chem. Intern. Ed. Engl.*, **4**, 872 (1965).
(8) R. B. Turner, *J. Am. Chem. Soc.*, **75**, 3484 (1953).
(9) K. Watanabe, C. N. Pillai, and H. Pines, *ibid.*, **84**, 3934 (1962).

Experimental Section

Melting points, determined using a Kofler micro hot stage, are corrected; boiling points are uncorrected. Microanalyses were by Galbraith Laboratories, Knoxville, Tenn. Infrared spectra were obtained with a Beckman IR-4 infrared spectrophotometer. Nmr spectra were obtained on a Varian A-60 spectrometer, and chemical shift values are given in parts per million relative to tetramethylsilane (internal standard). Gas chromatography was carried out at 170° on an F & M Model 770 gas chromatograph using a 2 ft × 0.25 in. copper column packed with 20% Carbowax 20 M on untreated[10] Chromosorb P. Yields were estimated by comparison of relative peak areas of the product in the weighed crude reaction mixture with those of the same sample volume of pure material.

1-Methyl-1-(1′-hydroxycyclopentyl)oxirane (**6**).—A solution of 20.6 g (0.12 mole) of *m*-chloroperbenzoic acid (F. M. C. Corp., 85%) in 200 ml of chloroform was added dropwise to a cold (ice bath), stirred solution of 12.6 g (0.10 mole) of 1-isopropenylcyclopentanol[2,3] in 50 ml of chloroform. The resulting solution was allowed to warm to room temperature and was stirred overnight. The mixture was then chilled in an ice bath, and the bulk of the *m*-chlorobenzoic acid removed by filtration. The filtrate was washed successively with aqueous solutions of sodium sulfite and sodium bicarbonate, dried over sodium sulfate, concentrated, and flash distilled at reduced pressure through a short-path distillation apparatus to yield 13.0 g of a colorless, sweet-smelling oil. Fractionation afforded 10.0 g (70%) of epoxide **6**: bp 82–83° (9 mm); $n^{25.2}$D 1.4686; ν_{max}^{neat} 3484, 2976, 2890, 1453, 1389, 1192, 1004, and 848 cm^{-1}.

Anal. Calcd. for $C_8H_{14}O_2$: C, 68.02; H, 9.79. Found: C, 68.28; H, 10.00.

1-Methyl-1-(1′-hydroxycyclobutyl)oxirane (**5**).—Epoxy alcohol **5** was prepared from 1-isopropenylcyclobutanol[3] in 80% yield by the same procedure as described above for the preparation of **6**. The pure material had bp 73–75° (6.5 mm); n^{25}D 1.4663; ν_{max}^{neat} 3460, 3012, 2959, 1255, 1232, and 901 cm^{-1}.

Anal. Calcd for $C_7H_{12}O_2$: C, 65.59; H, 9.44. Found. C, 65.76; H, 9.61.

1-Methyl-1-(1′-hydroxycyclohexyl)oxirane (**7**).—Epoxy alcohol **7** was prepared from 1-isopropenylcyclohexanol[2,3] in 85% yield as described above for epoxy alcohol **6**. It was obtained as a colorless oil: bp 97–98° (14 mm); $n^{25.4}$D 1.4721; ν_{max}^{neat} 3497, 2931, 2874, 1453, 1391, 1161, 975, and 843 cm^{-1}.

Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.33. Found: C, 69.40; H, 10.45.

Ring Expansion of Epoxy Alcohols (5–7). I. Reaction with Boron Trifluoride Etherate in Methylene Chloride. General Procedures.—To a stirred solution of 5 mmoles of the epoxy alcohol in 10 ml of methylene chloride cooled to *ca.* −5° with an ice–acetone bath, was added 0.21 ml, (1.67 mmoles 0.33 equiv) of boron trifluoride etherate *via* syringe. The solution was allowed to stir for 3–5 min during which time a pale yellow color developed. The reaction mixture was poured into ice water, the layers were separated, and the aqueous layer was extracted several times with methylene chloride. The organic phases were combined, washed with saturated sodium bicarbonate solution, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residual oils were analyzed directly by gas chromatography:

A. 2-Methyl-2-hydroxymethylcyclopentanone (**8**).—The preceding general procedure when applied to epoxy alcohol **5** produced 517 mg of a pale yellow oil. Gas chromatographic analysis indicated that keto alcohol **8** comprised 71% of this material for a yield of 63%. Distillation afforded pure **8** as a colorless oil: bp 110–113° (17 mm); $n^{24.3}$D 1.4666 [lit.[11] bp 103–108° (12 mm); n^{20}D 1.4681]; ν_{max}^{neat} 3448, 2976, 2882, 1739, 1468, and 1055 cm^{-1}.

B. 2-Methyl-2-hydroxymethylcyclohexanone (**9**).—The above general procedure was scaled up 20 times greater for the rearrangement of epoxy alcohol **6**. The crude product contained 6.96 g, 48% of keto alcohol **9** by gas chromatography. Distillation afforded 6.6 g (46.5%) of **9** as a colorless oil: bp 57–58° (0.5 mm), $n^{24.9}$D 1.4752 [lit.[12] bp 107–108° (11 mm); n^{20}D 1.4760].

(10) The use of bicarbonate washed support caused decomposition of the keto alcohols **8–10**, presumably *via* retroaldol deformylation.
(11) A. Eschenmoser and A. Frey, *Helv. Chim. Acta*, **35**, 1661 (1952).
(12) J. Colonge, J. Dreux, and H. Delaplace, *Bull. Soc. Chim. France*, 1635 (1956).

The semicarbazone crystallized as heavy needles from water, mp 153–158° (lit.[12] mp 155°).

The *p*-nitrobenzoate crystallized from petroleum ether (bp 20–40°), mp 64–66°.

Anal. Calcd for $C_{15}H_{17}NO_5$: C, 61.84; H, 5.88; N, 4.81. Found: C, 61.58; H, 5.83; N, 4.65.

C. 2-Methyl-2-hydroxymethylcycloheptanone (10).—Application of above general procedure produced an extremely viscous oil from epoxy alcohol **7**. Gas chromatographic analysis indicated the presence of only 15% of the desired keto alcohol **10** (see below).

II. Reaction with Acidic Alumina. General Procedure.—A mixture of 1 g of Merck acid-washed alumina in 20 ml of dry benzene was refluxed with stirring under a Dean–Stark trap for 12 hr. The solution was cooled slightly, and 1 mmole of epoxy alcohol was added. The resulting mixture was then refluxed with stirring for the specified period of time, cooled, and filtered. The alumina was washed with methylene chloride, the combined filtrate and washings were concentrated *in vacuo*, and the residual oil was analyzed by gas chromatography.

A. 2-Methyl-2-hydroxymethylcyclohexanone (9).—Employment of the above general procedure with a 2-hr reaction time, produced keto alcohol **9** in 52% yield as measured by gas chromatography.

B. 2-Methyl-2-hydroxymethylcycloheptanone (10).—The rearrangement of epoxy alcohol **7** was performed on a preparative scale. Thus, refluxing a benzene solution of 15.6 g (0.10 mole) of **7** with alumina overnight produced 11.9 g of a pale yellow oil, containing 7.65 g (49%) of keto alcohol **10** by gas chromatography. Distillation afforded 5.1 g (32.7%) of **10** as a colorless oil, bp 120–123° (8 mm). The semicarbazone melted at 148.5–150.5° after two recrystallizations from water.

Anal. Calcd for $C_{10}H_{19}N_3O_2$: C, 56.31; H, 8.98; N, 19.70. Found: C, 56.20; H, 9.03; N, 19.64.

The semicarbazone was hydrolyzed by warming in 10% sulfuric acid on a steam bath for 15 min. The reaction mixture was cooled and extracted with chloroform. The combined extracts were washed with saturated sodium chloride solution, dried, concentrated, and distilled to afford the pure keto alcohol **10**: bp 134–134.2° (16 mm); $n^{24.9}D$ 1.4827; ν_{max}^{neat} 3460, 2941, 2874, 1701, 1471, 1453, 1047, 1026 cm^{-1}.

Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.33. Found: C, 68.94; H, 10.37.

α-Amino Alkanoic and Alkenoic Acids with Perfluoroalkyl Terminal Segments[1]

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α-Amino acids bearing perfluoroalkyl groups were synthesized from perfluoroalkyl-substituted alkanoic acids by α bromination and α amination. Addition of 1-iodoperfluoropropane to ethyl alkenylacetamidomalonates and subsequent reactions gave alkenyl- and alkylmalonic acids having perfluoropropyl and acetamido substituents. The facile formation of γ lactones from such propenylacetamidomalonic acids was observed. Decarboxylation and hydrolysis then gave 5-perfluoropropyl-4-hydroxy-2-aminopentanoic acid, which readily re-formed the γ-lactone when converted to an N-trifluoroacetyl derivative. Synthesis of an heptafluoro-α-aminodecanoic acid from 1-iodoperfluoropropane and ethyl 4-pentenylacetamidomalonate was successfully demonstrated. High yields were secured in each step.

Free-radical addition of iodoperfluoroalkanes to alkenoic acids was used to prepare a series of long-chain iodoalkanoic acids having the general structure R_F-$CH_2CHI(CH_2)_nCOOH$, where R_F was a perfluoroalkyl group of one to ten carbons and n was an integer including 0–14. From these compounds the corresponding alkenoic acids [$R_FCH{=}CH(CH_2)_nCOOH$] and alkanoic acids [$R_F(CH_2)_{n+2}COOH$] were synthesized.[2]

$$R_FI + CH_2{=}CH(CH_2)_nCOOR \xrightarrow{R\cdot} RC_FH_2CHI(CH_2)_nCOOR$$

$$R_FCH_2CHI(CH_2)_nCOOR \xrightarrow[\text{alcohol}]{KOH} R_FCH{=}CH(CH_2)_nCOOH$$

$$\xrightarrow{HCl,\ Zn/\text{alcohol}} \quad \xrightarrow{H_2/Pt}$$

$$R_F(CH_2)_{n+2}COOH$$

The yields in each step were excellent with the exception of R_FI addition to acrylate esters where telomerization and low conversion resulted.[2,3] Very little is known about the corresponding α-amino acids bearing a terminal perfluoroalkyl group. Various alternative routes were explored in order to define a satisfactory procedure for the syntheses of these novel and potentially useful compounds.

Results

Two complementary methods were studied in some detail. The terminally fluorinated alkanoic acid prepared by the sequence given above was brominated and then aminated by standard procedures.[4,5] In each case the R_F group was perfluoropropyl, chosen for convenience and because of the availability of *n*-perfluoropropyl iodide.

$$R_F(CH_2)_nCH_2COOH + Br_2 \xrightarrow{PCl_3} R_F(CH_2)_nCHBrCOOH$$

$$R_F(CH_2)_nCHBrCOOH + NH_3 \xrightarrow[0°]{C_2H_5OH} R_F(CH_2)_nCHNH_2COOH$$

$$n = 2, 3$$

The yield of α-bromo acids (70%) was somewhat better than that of the α-amino acids (50–60%), but improvement in the latter undoubtedly could be made in view of the reported yield[5] of 95% for unfluorinated acids by this method. Displacement of bromine by azide ion also would appear to be useful.[6] The new α-amino acids were readily characterized, though they were very slightly soluble in water and were difficult to recrystallize. The N-trifluoroacetyl derivative was obtained in excellent yield by the method of Weygand and Geiger.[7]

(1) This work was carried out, in part, at the Illinois Institute of Technology during the summers of 1964 and 1965 under the National Science Foundation College Teacher Research Participation Program. Helpful discussions with Dr. Robert Filler are acknowledged.

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(4) J. F. Greenstein and M. Winitz, "Chemistry of the Amino Acids," Vol. 3, John Wiley and Sons, Inc., New York, N. Y., 1961, p 2382.

(5) S. Birnbaum, S. C. Fu, and J. P. Greenstein, *J. Biol. Chem.*, **203**, 333 (1953).

(6) H. M. Walborsky and M. E. Baum, *J. Org. Chem.*, **21**, 538 (1956).

(7) F. Weygand and R. Geiger, *Chem. Ber.*, **89**, 647 (1956).