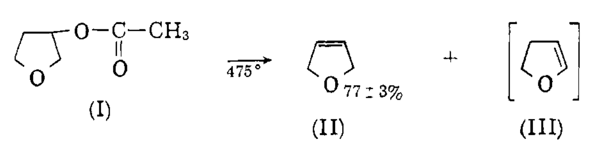
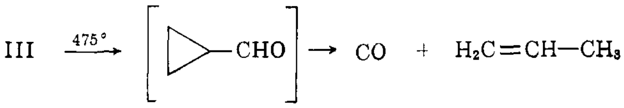
Of these few examples, two bear on the effect of an adjacent oxygen atom. Burchfield[2] found that on pyrolysis of the diacetate of propane-1,2-diol the secondary acetate was eliminated the more rapidly, and 75% of the olefinic product was allyl acetate and 25% propionaldehyde enol acetate. DePuy, King, and Froemsdorf[3,4] pyrolyzed 2-acetoxy-1-methoxypropane, and found an approximately 50–50 mixture of the 1- and 2-olefins to be formed.

A third ester with a beta oxygen has also been pyrolyzed. This ester is 3-acetoxytetrahydrofuran (I), which is readily prepared from the commercially available 3-hydroxytetrahydrofuran. Olsen[5] noted that pyrolysis of this ester gave no 2,3-dihydrofuran (III), but instead gave 3,4-dihydrofuran (II) and furan.



It had previously been shown, however, that 2,3-dihydrofuran decomposes when heated on glass[6] with the ultimate production of propylene and carbon monoxide. The following scheme has been suggested.



If this decomposition reaction of the enol ether were taking place during the pyrolysis reaction, a simple product analysis would give misleading results with respect to the direction of elimination. As a consequence we have re-examined this pyrolysis. At 475–500° only a single dihydrofuran is formed in the pyrolysis of I, and this olefin is 3,4-dihydrofuran, as shown by its spectral properties and its retention time on gas chromatography. In addition, two low-boiling products are formed, and these have been identified as propylene and carbon monoxide. We therefore believe that the 2,3-dihydrofuran is destroyed during the pyrolysis. In order to get an accurate measure of the relative amounts of the two olefins formed, we have made use of gas chromatography with an internal standard. A known mixture of the ester (I) and chlorobenzene was pyrolyzed to about 50% conversion. This conversion was determined accurately by the relative amounts of chlorobenzene and ester in the product. The amount of 3,4-dihydrofuran formed was also determined accurately from the chlorobenzene–olefin ratio in the product. By this method it was determined that pyrolysis of I gives 77 ± 3% of II. By difference it is assumed that the other 23% is III.

Experimental

3-Acetoxytetahydrofuran (I).—This ester was prepared from 3-hydroxytetrahydrofuran obtained from the Aldrich Chemical Company. Careful fractionation gave a fraction; b.p. 71.5–72.5°, 19 mm. [lit.,[7] b.p. 64° (2 mm.)].

3,4-Dihydrofuran (II).—This olefin was prepared by treating 2-butene-1,4-diol (25 g.) with sulfuric acid (1 g.) in a distilling flask at 20 mm. The product distilled as soon as formed, and was collected in a Dry Ice trap. Fractionation gave a pure fraction, b.p. 65–66° (lit.,[7] b.p. 67°).

Pyrolysis.—The pyrolyses were carried out as described previously.[3] In a typical run a mixture of 6.61 g. of chlorobenzene and 3.93 g. of I was analyzed by g.p.c. and the relative peak area determined. A portion of the mixture (3.27 g.) was pyrolyzed at 450°. At the temperature and flow rate chosen only about 50% conversion was obtained. A low boiling gas, identified as propylene by its g.p.c. retention time was obtained, along with higher boiling products. The higher boiling products were analyzed by g.p.c. using the chlorobenzene as an internal standard. From the decrease in ester–chlorobenzene ratio the amount of ester decomposed could be determined. From the olefin–chlorobenzene ratio the amount of 3,4-dihydrofuran was determined. Corrections were made for differences in thermal conductivities between the olefin and chlorobenzene, as determined by the analysis of known mixtures. By this method it was determined that pyrolysis of I gives 77 ± 3% II.

Gas Chromatography.—A 1-m. column of THEED[8] 1:3 on 60/80 firebrick in series with a 1-m. column of THEED on Fluoropak was used at 125°.

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[2] P. E. Burchfield, U. S. Patent 2,485,694 (1949); *Chem. Abstr.*, **44**, 2007 (1950).

[3] C. H. DePuy, R. W. King, and D. H. Froemsdorf, *Tetrahedron*, **7**, 123 (1959).

[4] C. H. DePuy and R. W. King, *Chem. Rev.*, **60**, 433 (1960).

[5] S. Olsen, *Acta Chem. Scand.*, **4**, 473 (1950).

[6] J. Wilson, *J. Am. Chem. Soc.*, **69**, 3002 (1947).

[7] W. Reppe, *Ann.*, **596**, 1 (1955).

[8] N,N,N',N'-Tetrakis(2-hydroxyethyl)ethylenediamine.

Half-lives of Some Inert Oxiranes in Acetic Acid–Pyridinium Hydrobromide at 30°

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Epoxysuccinic acids have been prepared by a variety of methods. Earlier stereochemical studies involved their interconversion to the corresponding chloromalic and tartaric acids.[1–3] Both the *trans*-racemate and the *cis,meso*-forms can be prepared from fumaric and maleic acids, respectively, by a sodium tungstate-catalyzed hydrogen peroxide oxidation.[4] The *cis,-meso*-form has been prepared also by the hydrogen peroxide oxidation of benzoquinone[5] and by nitric acid oxidation of the macrolide antibiotic, carbomycin.[6] To obtain the pure (−)-*trans* isomer, however, a fermentative preparation is convenient since good yields have been reported from the fermentation of dextrose by *Aspergillus fumigatus*.[7–10]

These prior publications, particularly some of the oxidative preparations and the formation of an acid chloride from the *cis* isomer by prolonged heating with phosphorus pentachloride,[11] suggested a remarkable

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[1] R. Kuhn and F. Ebel, *Ber.*, **58**, 926 (1925).

[2] R. Kuhn and R. Zell, *ibid.*, **59**, 2514 (1926).

[3] R. Kuhn and T. Wagner-Jauregg, *ibid.*, **61**, 513 (1928).

[4] G. B. Payne and P. H. Williams, *J. Org. Chem.*, **24**, 54 (1959).

[5] E. Weitz, H. Schobbert, and H. Seibert, *Ber.*, **68**, 1166 (1935).

[6] R. B. Woodward, *Angew. Chem.*, **69**, 50 (1957).

[7] J. H. Birkinshaw, A. Bracken, and H. Raistrick, *Biochem. J.*, **39**, 70 (1945).

[8] J. Moyer, U. S. Patent 2,674,561 (September 8, 1950), to the Secretary, Department of Agriculture.

[9] W. Martin and J. Foster, *J. Bacteriol.*, **70**, 405 (1955).

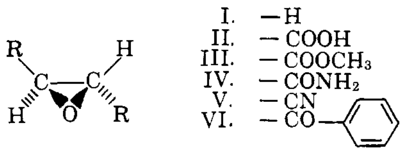
[10] It is interesting that fumagillin, another *Aspergillus fumigatus* metabolite, contains two epoxide groups: J. Landquist, *J. Chem. Soc.*, 4237 (1956), and D. S. Tarbell, R. M. Carman, D. D. Chapman, K. R. Huffman, and N. J. McCorkindale, *J. Am. Chem. Soc.*, **82**, 1005 (1960).

[11] C. Schöpf and W. Arnold, *Ann.*, **588**, 122 (1947).

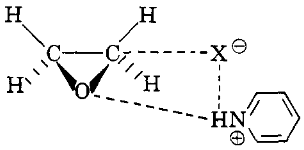
acid stability for the ethylene oxides so substituted.

We prepared (−)-*trans*-2,3-epoxysuccinic acid by the fermentation of crude molasses with *Aspergillus fumigatus*, and obtained a 40% molar yield based on the glucose content. A number of derivatives of the mold metabolite were prepared for structure-activity studies, and the impressive acid stability of this series of compounds seemed to be confirmed. It was possible, for example, to prepare esters by the ordinary Fischer technique, and to prepare the nitrile by heating the amide with phosphorus oxychloride.

Out of curiosity a comparison was made of the half-lives of several of the simpler derivatives in acetic acid–pyridinium hydrobromide at 30°. Since it was reputed to be an inert oxirane, *trans*-2,3-dibenzoylethylene oxide[12] was included in the measurements. An attempt was made to compare the compounds with ethylene oxide itself, but the latter proved too reactive for a rate determination under our conditions.



Pyridinium hydrobromide was used as a nonvolatile source of hydrobromic acid, but the pyridinium ion also participates importantly in the ring opening. In the cleavage of ethers by halogen halides it increases the rate.[13] In the anhydrous reaction of ethylene oxide with pyridine solutions of hydrogen halides an ion-pair complex has been proposed as the transition state, the formation of this complex being rapid, and its decomposition either by rearrangement to halogenohydrin or by attack of solvent molecules at carbon being the slow step responsible for the rate and the second-order kinetics observed.[14,15]



Results of the experiment are shown in Table I. The cleavage rate of epoxysuccinamide, the least reactive of the series, was one thirtieth as great as that of epoxysuccinonitrile and probably less than one thousandth as great as that of ethylene oxide.

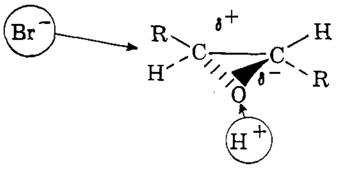
TABLE I

HALF-LIVES OF SOME INERT OXIRANES IN ACETIC ACID–PYRIDINIUM HYDROBROMIDE AT 30°

Compound	Half-life *t*/2, min.
Ethylene oxide[a]	<1
Epoxysuccinonitrile	65
Dibenzoylethylene oxide	305
Epoxysuccinic acid	1370
Methyl epoxysuccinate	1700
Epoxysuccinamide	1975

[a] Too small to measure by our method.

In an isotopic study of the acid-catalyzed hydrolysis of substituted ethylene oxides it was concluded that the cleavage and its rate determining step involved formation of a carbonium ion intermediate.[16,17]



If a similar mechanism can be assumed for the pyridinium hydrobromide–epoxide transition state, then the rate differences observed are consistent with the expected relative stabilities of the developing carbonium ions, nitrile and benzoyl groups being less effective carbonium ion stabilizers than carboxyl, carbomethoxyl, or carboxamide groups.

Other derivatives of (−)-*trans*-2,3-epoxysuccinic acid as well as some structure-activity relationships will be described elsewhere.[18]

Experimental[19]

Fermentative Conversion of Crude C Molasses to (−)-*trans*-Epoxysuccinic Acid.—An improved strain of *Aspergillus fumigatus* Fres. was used. Initially, the medium was based on those described in earlier publications (*e.g.*,[8]), and a medium from this patent is reproduced in Table II.

TABLE II

	g./l.
Glucose monohydrate	150.0
Beet molasses	20.0
Corn steep liquor	10.0
$MgSO_4 \cdot 7H_2O$	0.25
$(NH_4)_2SO_4$	.70
KH_2PO_4	.30
$ZnSO_4 \cdot 7H_2O$	.044
$CaCO_3$	30.0
Methanol	32.0

In still fermentations a period of 12 days at 30° was required. It was later found possible to use submerged fermentations for a shorter period with crude C molasses as the sole carbon source.

Isolation of Barium Epoxysuccinate.—A 130-gal. batch of fermentation whole broth was adjusted to a pH of 1.5 with concentrated hydrochloric acid, 10 lb. of filter aid (Super-Cel) added, and the mixture filtered through a small 12-plate filter press. To the filtrate, with stirring, was added 24 lb. of barium carbonate. The pH was adjusted to 7 with sodium hydroxide pellets, and stirring was continued for 10 hr. In this way 30.3 lb. (dry wt.) of barium epoxysuccinate was obtained. Barium analysis as $BaSO_4$: Calcd.: 51.4; Found, 51.2.

Conversion of Barium (−)-*trans*-Epoxysuccinate to (−)-*trans*-Epoxysuccinic Acid.—A 100-g. sample of barium epoxysuccinate, 85% purity, was suspended in 100 ml. of dry tetrahydrofuran and the temperature maintained at 5–10° while 18.5 ml. of concentrated sulfuric acid was added dropwise with stirring during 2.5 hr. The barium sulfate was removed, washed with fresh cold solvent, and the filtrate evaporated to give 40 g. of dry, tan crystalline epoxysuccinic acid, of 95% purity (95% yield), as well as 5.24 g. of a gummy residue. One recrystallization from dry dioxane gave nearly pure white crystals, m.p. 182–184°; with little loss. $[\alpha]^{25}_{D}$ −118° (*c*, 1.0 in ethanol).

Anal. Calcd. for $C_4H_4O_5$: C, 36.38; H, 3.05. Found: C, 36.43; H, 3.11.

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(17) J. G. Pritchard and F. A. Long, *ibid.*, **78**, 6008 (1956).

(18) M. W. Miller, *J. Med. Chem.*, **6**, 00 (1963).

(19) Melting points were determined on a calibrated Kofler micro hot stage.

When acetone was used as the acidification solvent, a 66% yield was obtained. When water was used, the yield was 60%.

Dimethyl (−)-*trans*-Epoxysuccinate (III) from Barium (−)-*trans*-Epoxysuccinate.—A 2000-g. sample of 85% pure barium epoxysuccinate (6.36 moles) was suspended in 6 l. (149 moles) of dry methanol. The mixture was cooled to 10–15° and 452 ml. (832 g. of 8.49 moles) of concentrated sulfuric acid added slowly with stirring during 4 hr. After standing overnight 240 g. (2 moles) of anhydrous magnesium sulfate was added and the mixture refluxed with stirring for 5 hr. Upon addition of 187 g. (1.87 moles) of powdered calcium carbonate the temperature was raised to 60°, the methanol solution filtered through a heated funnel, and the solvent removed at reduced pressure.

In this way 820 g. (5.12 moles) of ester was obtained as a first crop and 92 g. by sublimation or recrystallization of the residue for a 96% yield of nearly pure white dimethyl epoxysuccinate, m.p. 72–75°. Sublimation at 50–80° (2 mm.) yielded large colorless needles, m.p. 74–75°. $[\alpha]^{25}_D$ −125° (*c*, 1.0 in ethanol).

Anal. Calcd. for $C_6H_8O_5$: C, 45.00; H, 5.04. Found: C, 45.03; H, 5.14.

Methyl (−)-*trans*-epoxysuccinate also was prepared in 70–75% yields by Fischer esterification of the free acid.

Preparation of (−)-*trans*-Epoxysuccinamide (IV) from Dimethyl (−)-*trans*-Epoxysuccinate.—A 70.0-g. sample (0.437 mole) of dimethyl epoxysuccinate was stirred with 200 ml. of cold ammonium hydroxide (29% ammonia), using a strong stirrer in an open beaker for 10–15 min. The ester dissolved as the amide separated, and the product was removed by filtration and washed with a little cold water. The crude dry epoxysuccinamide weighed 60 g., m.p. 203–206°. Recrystallization from water gave 52 g. (97% yield) of pure material, m.p. 205–208° dec. $[\alpha]^{25}_D$ −68° (*c*, 1.0 in water).

Anal. Calcd. for $C_4H_6N_2O_3$: C, 36.92; H, 4.65; N, 21.54. Found: C, 36.67; H, 4.40; N, 21.59.

(−)-*trans*-Epoxysuccinonitrile (V) from (−)-*trans*-Epoxysuccinamide.—A stirred mixture of 5.4 g. (0.0415 mole) of dry epoxysuccinamide and 30 ml. of phosphorus oxychloride was heated rapidly under dry nitrogen. During 35 min. the amide dissolved as the temperature of the oil bath was raised from 80–100°, and 5 min. later heating was discontinued. After cooling to room temperature, excess phosphorus oxychloride was removed by distillation at 10-mm. pressure (water aspirator), and epoxysuccinonitrile separated as the concentration progressed. The crude product was removed by filtration, sucked very dry, washed twice with ice–water, and purified by sublimation at 85° (0.1 mm.). The purified substance, 1.9 g. (49% yield) formed thick white prisms, m.p. 130–130.5°. $[\alpha]^{25}_D$ −71° (*c*, 1.0, ethanol).

Anal. Calcd. for $C_4H_2N_2O$: C, 51.06; H, 2.14; N, 29.78. Found: C, 51.10; H, 1.92; N, 29.29.

Many other techniques of nitrile formation failed when applied to (−)-*trans*-epoxysuccinamide.

Determination of the Half-lives of 1,2-Disubstituted Ethylene Oxides in Acetic Acid Solution with Pyridine Hydrobromide at 30°.—Pyridine hydrobromide was used as a nonvolatile source of hydrobromic acid. The pyridine released during reaction of the hydrobromic acid with the epoxide was measured by potentiometric titration of aliquots at intervals with perchloric acid. The acetic acid solutions were maintained at 30° ± 0.1° in a thermostat-controlled water bath.

In the determinations in Table III, *a* is the millimolar concentration of the epoxide, *b* is the millimolar concentration of pyridine hydrobromide, and *x* is the millimolar quantity of epoxide consumed at *t* minutes.

TABLE III

TITRATIONS AND CALCULATIONS FOR DETERMINATION OF THE HALF-LIFE OF EPOXYSUCCINIC ACID IN PYRIDINIUM BROMIDE–ACETIC ACID AT 30°

t, min.	V_{cor}, ml.	x	$a - x$	$b - x$	$\frac{a\ b - x}{b\ a - x}$
0	0.000	0.0000	0.0906	0.5000	1.00
242	.060	.0098	.0808	.4902	1.10
1376	.277	.0455	.0451	.4549	1.83
1809	.324	.0532	.0374	.4468	2.16

Log $[a\ (b - x)/b\ (a - x)]$ was plotted against time to give second-order curves, and the slopes of these curves were substituted into the second-order rate equation to determine half-times. For example, a 59.8-mg. sample of epoxysuccinic acid (mol. wt. 132) was dissolved in 25 ml. of acetic acid. This was mixed with 25 ml. of 0.1 *M* pyridine hydrobromide in acetic acid. The solution was immersed in a water bath at 30°, and 10-ml. aliquots were withdrawn at intervals *t* and titrated potentiometrically with 0.1635 *N* perchloric acid. Blanks were treated similarly.

Acknowledgment.—The authors are grateful to Dr. D. B. Seeley for the fermentative preparation of the epoxysuccinic acid, to Glenn Hess for the half-life titrations, and to Charles Scott for technical assistance.

Derivatives of Primary Nitroalkanes. Preparation of Isoxazolines

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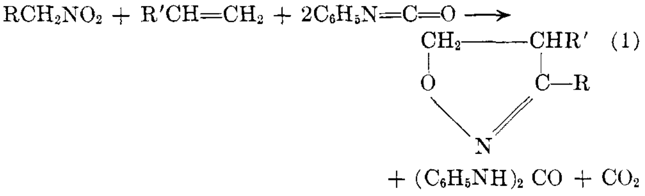
Although various methods[1–5] have been used for derivative formation and identification of primary nitroalkanes, none of these possesses the advantages of producing crystalline solids with sharp melting points in a single stage reaction. In seeking such a method our attention was directed to the recent work of Mukaiyama and Hoshino[6] in which they treated primary nitroalkanes with phenyl isocyanate in the presence of various olefins, using a tertiary amine as a catalyst, and obtained the corresponding substituted isoxazolines.



$RCH_2NO_2 + R'CH{=}CH_2 + 2C_6H_5N{=}C{=}O \longrightarrow$ (1)

$+ (C_6H_5NH)_2CO + CO_2$

Nitrile oxides are the probable intermediates. Most of the compounds prepared were liquids or low melting solids unstable to heat; nevertheless, the method possesses merit because it is simple and direct and seems capable of development into a satisfactory method for routine derivative formations.

Not all olefins give isoxazolines by this procedure, and many which do react give very low yields of isoxazolines. The unsuitability of many olefins for this type of reaction was demonstrated by the unsatisfactory results obtained with hexachlorocyclopentadiene, cyclohexene, and cholesteryl acetate using phenyl isocyanate, 1-nitrobutane, and triethylamine. Dipropylfuroxane (from dimerization of butanenitrile oxide) was the only reaction product which could be isolated from all three reactions. Unconjugated double bonds in six-membered rings were

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