sealed stirrer, and dropping funnel, and covered with ether. Ethyl bromide (7.4 g., 0.068 mole) in 100 ml. ether was added dropwise and the reaction mixture boiled for 1 hr. 3-Methoxy-3-methyl-1-butyne (4.9 g., 0.05 mole), dissolved in 70 ml. of ether, was then added dropwise with stirring. The mixture was boiled for 4 hr., cooled, and 9.4 g. (0.05 mole) of benzophenone dissolved in 100 ml. of ether was added dropwise with stirring in 30 min. The reaction mixture was stirred overnight at room temperature, boiled for 4 hr., cooled, and hydrolyzed by slow addition of 100 ml. of ice water. Approximately 10 g. of ammonium chloride was added in portions with stirring to the suspension until two clear layers separated. The ethereal layer was separated, washed with two 200-ml. portions of cold water and dried over anhydrous potassium carbonate.

The ether was removed by distillation leaving an oily residue which solidified on standing. The solid was dissolved in boiling petroleum ether (b.p. 60–90°) and on cooling, white needles precipitated. The precipitate was collected by filtration and dried; 8.5 g. (61% yield), m.p. 87–89.5°. Two recrystallizations from petroleum ether gave white needles, m.p. 85–86.5°.

Anal. Calcd. for $C_{19}H_{20}O_2$: C, 81.40; H, 7.19. Found: C, 81.51; H, 7.07.

The infrared spectrum had bands at 2.8, 4.5, and 8.5 μ for —OH, —C≡C—, and tertiary C—O respectively.

4-Methoxy-4-methyl-2-pentynoic acid. Ethylmagnesium bromide was prepared from 37 g. (0.34 mole) of ethyl bromide and 8 g. (0.33 g.-atom) of magnesium turnings in ether in a 1-l., three-neck flask fitted with mercury sealed stirrer, dropping funnel, and reflux condenser. Twenty-four grams (0.25 mole) of 3-methoxy-3-methyl-1-butyne in 100 ml. of ether was added dropwise with stirring over a period of 2 hr. The mixture was boiled for 3 hr. and then cooled to room temperature. The dropping funnel was replaced by a gas inlet tube and carbon dioxide, dried with sulfuric acid, was admitted for 16 hr. with stirring. The mixture was hydrolyzed with 200 ml. of ice water and *ca.* 300 ml. of 10% hydrochloric acid. The mixture was stirred until two clear layers were formed. The lower layer was withdrawn and extracted with two 100-ml. portions of ether. The ether extracts were combined and washed with three 100-ml. portions of water and dried over anhydrous sodium sulfate. After evaporation of the ether, the dark residue was distilled and gave 14.6 g. (41% yield) of a viscous liquid, b.p. 99–103°/0.5 mm., n_D^{25} 1.4580. This liquid, which turned yellow shortly after distillation, was soluble in water, 10% sodium hydroxide solution, and evolved carbon dioxide when added to a 10% sodium bicarbonate solution.

The *p-phenylphenacyl ester* was prepared by adding 10% sodium hydroxide dropwise to a mixture of 5 ml. of water and 1 g. of the acid contained in a 50 ml. round-bottom flask fitted with reflux condenser until the solution was neutral. Two drops of the acid were then added to make the solution slightly acidic. Ethanol (10 ml.) and 1 g. of *p*-phenylphenacyl bromide were added and the mixture was boiled for 2 hr. The hot solution was transferred to a 50 ml. beaker and cooled overnight. The needles which precipitated were recrystallized three times from 60% ethanol; m.p. 102.5–104°.

Anal. Calcd. for $C_{21}H_{20}O_4$: C, 74.98; H, 5.99. Found: C, 74.70; H, 6.26.

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NOTRE DAME, IND.

[CONTRIBUTION FROM THE EASTERN REGIONAL RESEARCH LABORATORY[1]]

Glycidyl Esters. I. Method of Preparation and Study of Some Reaction Variables[2]

GERHARD MAERKER, JOAN F. CARMICHAEL, AND WILLIAM S. PORT

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The reaction of stearic acid, azelaic acid, and the sodium salts of both acids with excess epichlorohydrin in the presence of benzyltrimethylammonium chloride has been studied. Use of the free carboxylic acids gave only fair to low yields of glycidyl esters, while sodium salts of the carboxylic acids gave excellent yields of materials of high oxirane content. Crude glycidyl stearate was obtained in greater than 90% yield in a nonaqueous, but not anhydrous, system. Crude diglycidyl azelate was prepared in 55% yield from an aqueous solution of disodium azelate. Recrystallization of both crude glycidyl esters raised their purity above 95%. Reaction time, reaction temperature, and water content were found to influence the yield of glycidyl stearate. It is suggested that the reaction path involves nucleophilic attack upon the terminal position of the epoxide. The resulting alkoxide then reacts further to give either a glycidyl ester or a chlorine-containing by-product, the predominant course depending upon reaction conditions.

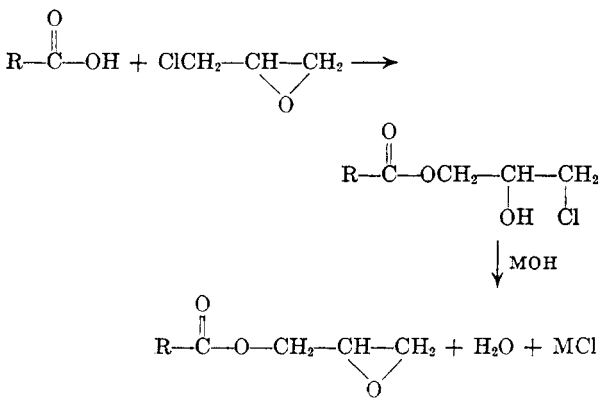
As part of a study of the preparation and properties of epoxy derivatives of fatty materials, it was desired to prepare the glycidyl esters of several aliphatic mono- and dicarboxylic acids. Although a number of methods for the synthesis of such esters has been reported, many of the procedures are cumbersome, require uncommon or expensive reagents or give the desired product in low yield.

The more common starting materials for the preparation of glycidyl esters have been epichlorohydrin and the carboxylic acid or its salt, although the direct esterification of glycidol with acid chlo-

(1) Eastern Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture.

(2) Presented in part at the 34th fall meeting of the American Oil Chemists' Society, October 17–19, 1960, New York, N. Y.

rides in the presence of base has been reported.[3-5] The reaction of monocarboxylic acids with epichlorohydrin,[6] especially in the presence of catalysts of the Friedel-Crafts type,[7,8] or of basic organic nitrogen compounds[9,10] results in the formation of α-carboxylic esters of γ-chloropropylene glycol which are then dehydro-halogenated in the presence of strong base to give the desired glycidyl ester.



Mueller[11] reported that the glycidyl ester can be obtained directly if epichlorohydrin is in large excess and if a quaternary ammonium halide is used as catalyst. The hydrogen chloride eliminated in the reaction is largely absorbed by the excess epichlorohydrin to form glycerol dichlorohydrin, but at least some of the hydrogen chloride is likely to react with the glycidyl ester present to give the α-carboxylic ester of β- or γ-chloropropylene glycol.

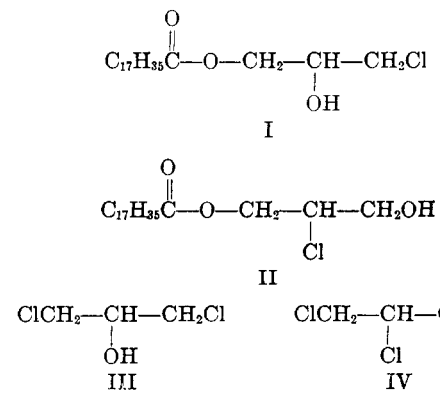
To avoid the troublesome problem of secondary reactions of glycidyl esters with hydrogen chloride, some workers used salts of carboxylic acids, rather than the acids themselves, as starting materials. Kester[5,12] obtained good conversions to glycidyl esters of mono-, but not of dicarboxylic acids, by refluxing mixtures of salts of long-chain fatty acids with epichlorohydrin, taking elaborate precautions to exclude all traces of moisture. Addition of a quaternary ammonium halide was reported to increase the rate of this reaction also,[13] but even small amounts of water decreased yields of oxirane-containing products,[14] while in partly aqueous medium the formation of glycidyl esters occurred either in very low yield[15] or not at all.[16]

As an initial step in the preparation of glycidyl esters of various mono- and dicarboxylic acids, a better understanding of the reaction of epichlorohydrin with carboxylic acids and their salts was needed. Stearic acid and azelaic acid were chosen as representatives of the two classes of acids, and their reaction with epichlorohydrin was investigated under various reaction conditions. The influence of reaction temperature, moisture content, and reaction time were of particular interest.

RESULTS

A. The reaction of epichlorohydrin with stearic acid. In refluxing epichlorohydrin containing benzyltrimethylammonium chloride (BTM), stearic acid was consumed in a few minutes, and the main product, glycidyl stearate, was obtained in 70% yield. At lower temperatures more time was required for complete consumption of stearic acid, the yield of glycidyl stearate decreased sharply, and the major product was an ester which contained chlorine (Table I). A decrease in glycidyl stearate yield, accompanied by an increase in the formation of chlorinated esters, was also observed when the reaction mixture contained considerable amounts of water. This effect was small, however, when the moisture content was low.

Separation of the crude reaction mixture into its major components revealed the chlorinated ester to be 3-chloro-2-hydroxypropyl stearate (I) probably in admixture with a small amount of its isomer 2-chloro-3-hydroxypropyl stearate (II). A considerable amount of glycerol α-dichlorohydrin (III), possibly containing small amounts of its isomer (IV), was also present in the reaction



mixture. A quantitative separation of the "chlorohydrin esters" (I and II) from glycidyl stearate was not achieved, but a procedure was devised for estimating the relative amounts of the two types of esters in the crude product. Crystallization from

(3) F. Zetsche and F. Aeschlimann, *Helv. Chim. Acta*, **9**, 708 (1926).
(4) Henkel and Cie., British patent **735,001**, Aug. 10, 1955.
(5) E. B. Kester, C. J. Gaiser, and M. E. Lazar, *J. Org. Chem.*, **8**, 550 (1943).
(6) M. J. Viard, French patent **1,011,410**, June 23, 1952.
(7) E. Knoevenagle, *J. Chem. Soc.*, AI, 163 (1914).
(8) G. Stein, U. S. patent **2,224,026**, Dec. 3, 1940.
(9) G. Stein, German patent **708,463**, June 12, 1941.
(10) E. C. Shokal and A. C. Mueller, U. S. patent **2,895,947**, July 21, 1959.
(11) A. C. Mueller, U. S. patent **2,772,296**, Nov. 27, 1956.
(12) E. B. Kester and H. M. Preusser, U. S. patent **2,448,602**, Sept. 7, 1948.
(13) P. Edwards, U. S. patent **2,537,981**, Jan. 16, 1951.
(14) R. Kohler and H. Pietsch, German patent **944,995**, June 28, 1956; British patent **766,771**, Jan. 23, 1957.
(15) G. L. Dorough, U. S. patent **2,524,432**, Oct. 3, 1950.
(16) R. J. Chamberlain, U. S. patent **2,893,875**, July 7, 1959.

TABLE I

REACTION OF STEARIC ACID AND EPICHLOROHYDRIN.[a] EFFECT OF REACTION TEMPERATURE AND ADDITION OF WATER

Temp.	Time, Hr.	Added Water Content of Reaction Mixture Mole Per Cent	Glycidyl Stearate in Crude Product: Yield, %[b,c]	Glycidyl Stearate in Crude Product: Concentration, %[c]	Recrystallized Reaction Product: Glycidyl stearate concentration, %[c]	Recrystallized Reaction Product: "Chlorohydrin ester" concentration, %[d]
117	0.5	None	70.0	63.8	78.7	14.6
117	0.5	2.0	64.6	61.9	69.1	24.6
92	0.5	None	27.1	24.7	27.0	67.3
91	1.5[e]	41.1	11.4	10.4	9.6	86.7
60	5.0[e]	None	7.8	7.5	5.6	92.2

[a] Molar ratio of epichlorohydrin:stearic acid:BTM = 8:1:0.027. [b] Based on stearic acid. [c] Based on oxirane determination by method of Durbetaki.[21] [d] Based on chlorine content. [e] Time required for complete consumption of stearic acid.

TABLE II

REACTION OF SODIUM STEARATE AND EPICHLOROHYDRIN.[a] EFFECT OF REACTION TEMPERATURE IN PRESENCE AND ABSENCE OF ADDED WATER

Temp.	Time, Hr.	Added Water Content of Reaction Mixture Mole Per Cent	Sodium Stearate Consumed, %	Crude Product: Glycidyl Stearate: Yield, %[b,c]	Crude Product: Glycidyl Stearate: Concentration, %[c]	Crude Product: "Chlorohydrin ester" concentration, %[d]
117	0.16	None	98.9	90.0	90.4	4.3
92	0.16	None	56.6	83.0	82.3	11.7
92	0.5	41.1	100.0	82.4	81.1	21.7
75[e]	1.5	None	60.0	79.9	75.5	26.5
75	1.5	41.1	100.0	75.1	76.4	17.1
60	4.5	None	34.0	76.6	72.7	28.9
60	4.5	41.1	80.0	62.3	60.4	37.5

[a] Molar ratio of epichlorohydrin:sodium stearate:BTM = 16:1:0.1. [b] Based on consumed sodium stearate. [c] Based on oxirane determination by method of Durbetaki.[21] [d] Based on chlorine content. [e] Reflux temperature of reaction mixture.

solvents which dissolved nonester impurities gave a mixture of esters which was analyzed for oxirane content, chlorine content, and saponification number. It was assumed that only glycidyl stearate and "chlorohydrin ester" were present in significant amounts, and an estimation was made from the analytical data of the amounts of each type of ester (see Table I). Although small amounts of other esters, such as glyceryl monostearate, were also found in the mixed esters, glycidyl stearate, and "chlorohydrin esters" together accounted for well over 90% of the mixture.

Optimum catalyst concentration was not determined. In the absence of catalyst, 90% of the stearic acid was recovered after 5 hours refluxing with epichlorohydrin, showing a large catalyst effect. Other quaternary ammonium halides gave, with the exception of tetraethylammonium bromide, significantly lower yields than benzyltrimethylammonium chloride, probably because of lower solubility in epichlorohydrin.

B. Reaction of epichlorohydrin with azelaic acid. The reaction of epichlorohydrin with azelaic acid in the presence of benzyltrimethylammonium chloride proceeded in a manner similar to that with stearic acid. Analysis of the crude product by oxirane determination showed a conversion of 64% of the acid groups to the glycidyl ester, the balance of the acid groups presumably reacting to give the "chlorohydrin ester."

The crude product therefore contained a mixture of diglycidyl azelate (V), glycidyl 3-chloro-2-hydroxypropyl azelate (VI), and bis(3-chloro-2-hydroxypropyl) azelate (VII) and possibly the isomers of VI and VII in which the positions of the chlorine and hydroxyl groups are reversed. No efforts were made to isolate compounds VI and VII in the pure state, but their presence was indicated from analytical data and from analogy to the reaction of epichlorohydrin with stearic acid. From the measured 64% conversion of the acid groups to glycidyl ester and with the assumption of a statistical distribution, the amount of desired diglycidyl azelate (V) in the crude mixture was calculated to be 30.4 weight per cent, and VI and VII 49.6 and 19.9 weight per cent, respectively. The yield of the desired product (V) could undoubtedly be increased by dehydrohalogenation[6,10] of compounds VI and VII.

C. Reaction of epichlorohydrin with sodium stearate. Glycidyl stearate was obtained in 90% or higher yields when sodium stearate rather than stearic acid, was caused to react with epichlorohydrin at reflux in the presence of benzyltrimethylammonium chloride. The reaction was extremely fast, almost all of the sodium stearate having been consumed

within five to ten minutes after catalyst addition. (However, to insure completeness of reaction, the mixture was heated for thirty minutes in some of the experiments.[17]) At lower temperatures, the reaction proceeded more slowly so that at 60° considerable amounts of unreacted sodium stearate were recovered even after four and a half hours of heating. The precautions for dryness required for the uncatalyzed reaction[5] were not needed when catalyst was used, although the absence of moisture probably would improve yields somewhat.

The effect of reaction temperature in the presence and absence of added water was tested (Table II). Water increased the rate of consumption of sodium stearate, but decreased its conversion to glycidyl stearate. Lowering of the reaction temperature decreased both the rate of sodium stearate consumption and the conversion of consumed sodium stearate to glycidyl stearate. This behavior is the same as that observed in the reaction of stearic acid. In further analogy to the reaction of stearic acid, the only major product obtained in addition to glycidyl stearate was the "chlorohydrin ester," the two types of esters again accounting for essentially all of the starting material. The data indicate that "chlorohydrin ester" formation is favored by low reaction temperatures and the presence of water.

Significantly, and in contrast to the reaction of stearic acid, the reaction of sodium stearate and epichlorohydrin did not give rise to the formation of glycerol chlorohydrins. It was therefore unnecessary to recrystallize the crude product before the "chlorohydrin ester" content was determined.

In order to determine the effect of prolonged heating upon the reaction mixture, stearic acid and sodium stearate were each refluxed with epichlorohydrin for one-half hour and for five hours in the presence of benzyltrimethylammonium chloride. Analysis of the crude and of the recrystallized product revealed that prolonged heating causes the destruction of some of the glycidyl stearate formed initially and gives rise to oxirane-containing by-products not found after brief heating.

The oxirane-containing impurities arise from an autoreaction of epichlorohydrin in the presence of benzyltrimethylammonium chloride. A mixture of such compounds was isolated after allowing epichlorohydrin to reflux in the presence of benzyltrimethylammonium chloride for six hours. Significant amounts of these products were not found after heating a similar solution at 100° for three hours. The number of components of this mixture has not yet been established, but it is known that nitrogen is absent, that the empirical formula of the combined impurities is close to that of epichlorohydrin and that the boiling range of the mixture is considerably above that of epichlorohydrin. Studies on this problem are continuing.

While the autoreaction of epichlorohydrin was of minor importance in the preparation of glycidyl stearate, because of the short reflux periods required, its significance was much greater in the preparation of diglycidyl azelate.

D. Reaction of epichlorohydrin with disodium azelate. When epichlorohydrin, disodium azelate, and benzyltrimethylammonium chloride were heated at reflux for one-half hour, no oxirane-containing product could be isolated, and most of the disodium azelate was recovered unchanged. Heating the reaction mixture at reflux for six hours gave crude diglycidyl azelate having low purity and containing impurities arising from the autoreaction of epichlorohydrin. Recovery of pure diglycidyl azelate from this mixture was not readily accomplished.

The low reactivity of disodium azelate was ascribed to low solubility in epichlorohydrin, resulting in poor contact of the two reagents. Improvement of contact was achieved by dissolving disodium azelate in water before combining it with epichlorohydrin. As a result, all of the disodium azelate was consumed and the reaction completed in less than an hour giving fair conversions to crude products which were easily purifiable.

The use of water in this reaction is contrary to the recommendations of previous workers in this field and, in fact, is contraindicated by the studies already described. However, the need for improved contact between epichlorohydrin and disodium azelate to shorten reaction time, coupled with the relatively low yield losses experienced in similar experiments with sodium stearate, prompted the use of a partly aqueous system in this case. It is conceivable that other methods can be found to improve contact and shorten reaction time. Two obvious methods are the use of a higher reaction temperature under pressure and the employment of a noninterfering mutual solvent for sodium azelate and epichlorohydrin. These, however, were not tried in the present work.

Three procedures, differing only slightly in detail, were used to combine the aqueous disodium azelate with epichlorohydrin and catalyst. Best yields were obtained by slow addition of the hot aqueous solution to boiling epichlorohydrin and removal of the water continuously as the epichlorohydrin azeotrope. The rate of water removal was somewhat slower than the rate of addition, and the temperature of the reaction mixture decreased slowly as the water content of the mixture increased. The reaction was stopped when all of the aqueous azelate had been added and almost all of the water had again been removed. In modifications of this procedure, the water added slowly as azelate solution was kept in the reaction mixture at total reflux,

(17) According to Kester *et al.*,[5] the uncatalyzed reaction requires twelve hours at reflux with rigorous exclusion of moisture to form glycidyl stearate in unstated yield.

or the aqueous azelate was added as one batch and the mixture refluxed. The higher yields obtained by the first method were ascribed to the higher reaction temperature, especially during the early part of the addition when water concentration in the mixture was low.

This temperature dependency, noted previously in the reactions of stearic acid and sodium stearate, was shown to hold also for the reaction of disodium azelate with epichlorohydrin (see Table IV). In the study of this effect the batch mix method of contact was chosen for convenience in temperature regulation. Again, lowering of the reaction temperature increased the time required for complete consumption of carboxylate and decreased conversion to the desired product.

TABLE III

REACTION OF SODIUM STEARATE OR STEARIC ACID AND EPICHLOROHYDRIN.[a] EFFECT OF HEATING PERIOD

Starting Material	Period at Reflux, Hr.	Crude Glycidyl Stearate		Once-crystallized Glycidyl Stearate	
		Conversion, %[b]	Concentration, %[b]	Conversion, %[b]	Concentration, %[b]
Sodium stearate	0.5	93.3[c]	89.6	76.4[c]	92.3
Sodium stearate	5.0	93.0[c]	81.1	66.4[c]	83.8
Stearic acid	0.5	70.0[d]	63.8	58.5[d]	78.7
Stearic acid	5.0	63.4[d]	54.5	41.4[d]	68.3

[a] Reagent ratios as in Tables I and II. [b] Based on oxirane determination by method of Durbetaki.[21] [c] Based on sodium stearate. [d] Based on stearic acid.

TABLE IV

REACTION OF AQUEOUS DISODIUM AZELATE WITH EPICHLOROHYDRIN.[a,b] INFLUENCE OF REACTION TEMPERATURE

Reaction Temp.	Reaction Time, Hr.[c]	Crude Product	
		Oxirane Oxygen, %[d]	Conversion to Glycidyl Ester, %[d]
92–94.5	0.5	6.95	68.2
70	2.5	5.93	61.0
60	4.5	5.27	51.1

[a] Aqueous azelate added batchwise–added water retained. [b] Molar ratio of epichlorohydrin:disodium azelate (33% aq.):BTM = 7:1:0.2. [c] Required for complete consumption of disodium azelate. [d] Based on oxirane determination by method of Durbetaki.[21]

DISCUSSION

Although elucidation of a reaction mechanism is not within the scope of the present paper, certain inferences regarding the site at which epichlorohydrin is attacked by carboxylate may be drawn from some of the reported observations. The latter include the formation "chlorohydrin ester" in both acid (stearic acid) and neutral (sodium stearate) medium, the formation of glycerol dichlorohydrin in acid medium only and the decrease in glycidyl ester yield, and simultaneous increase in "chlorohydrin ester" yield, at lower reaction temperatures and in the presence of water. Glycidyl ester formation may occur either by direct displacement of chloride by carboxylate, the oxirane ring remaining intact throughout the reaction (path A) or by attack of the carboxylate ion on the terminal carbon of the oxirane ring giving rise to an intermediate alkoxide ion which subsequently reforms the oxirane ring by displacement of chlorine (path B).

If path A pertains, the appearance of "chlorohydrin ester," and also of glycerol dichlorohydrin, may be due to secondary addition of the elements of hydrogen chloride to glycidyl stearate and epichlorohydrin, respectively. In acid medium, where protons and chloride ions are products of the primary reaction, such secondary additions are to be expected. In neutral medium, however, where protons are not produced in the primary reaction, the formation of "chlorohydrin ester," and particularly when not accompanied by the simultaneous appearance of glycerol dichlorohydrin, is inconsistent with path A. Moreover, the formation of "chlorohydrin ester" as the principal reaction product at lower temperatures in acid medium (see Table I) would require, by path A, that under these conditions hydrogen chloride adds to the glycidyl ester with considerably greater ease than it adds to epichlorohydrin which is present in eightfold excess. At the reflux temperature, on the other hand, the preference of addition would have to be the reverse, *i.e.*, in favor of epichlorohydrin, since the glycidyl ester is the major reaction product. From the known properties of glycidyl esters and epichlorohydrin it is difficult to rationalize this behavior.

On the other hand path B represents a well known reaction of nucleophilic reagents.[18] Alkoxide ions of the type hypothesized appear to have considerable stability.[19,20] "Chlorohydrin ester" is formed when the alkoxide ion captures a proton, the likelihood of the latter reaction depending upon the availability of protons in the reaction medium. Consequently, more "chlorohydrin ester" would be expected to be formed by this path in acid medium than in neutral medium where the probable source of protons is any water which may be present. The experimental findings are in accordance with this hypothesis.

It is consistent with path B that in neutral medium, where proton availability is low, glycerol dichlorohydrin is not found, since, in contrast to the

(18) R. E. Parker and N. S. Isaacs, *Chem. Revs.*, **59**, 737 (1959).

(19) P. Ballinger and F. A. Long, *J. Am. Chem. Soc.*, **81**, 2347 (1959).

(20) C. G. Swain, A. D. Ketley, and R. F. W. Bader, *J. Am. Chem. Soc.*, **81**, 2353 (1959).

more basic alkoxide ion, epichlorohydrin is incapable of abstracting protons from water.

The observed increased production of "chlorohydrin ester" at lower reaction temperatures again can be rationalized on the basis of path B. Nucleophilic displacement reactions such as the initial opening of the epoxide ring by carboxylate and the formation of the new epoxide ring by displacement of chlorine are expected to have the normal significant temperature dependence, while proton capture, essentially an acid-base reaction, would be affected relatively little. At the lower reaction temperatures, then, ring closure has been slowed down sufficiently to allow proton capture to become the predominating reaction.

The above considerations lead to the conclusion that the experimental data now available are in better agreement with path B than path A. However, in the absence of further information a final conclusion regarding the point of attack must be deferred. It is hoped that studies which are presently in progress will help to shed further light on this question.

EXPERIMENTAL

Materials. Stearic acid. Stearic acid (Humko Hystrene m.p. 65–66.5°, Acid No. 197.6) was recrystallized twice from acetone at 2° to obtain purified stearic acid (m.p. 69.3–70.0°, Acid No. 196.9).

Azelaic acid. Azelaic acid (Emery—Recrystallized) was recrystallized twice from water. The resulting moist solid was placed into toluene, water was removed as toluene azeotrope, and the toluene solution was cooled and filtered. Drying in the vacuum oven gave refined azelaic acid (m.p. 105.3–107.3°, Acid No. 596.1).

Sodium stearate. The method used was essentially that of Kester, *et al.* (5).

Disodium azelate. The preparation was analogous to that of sodium stearate.

Epichlorohydrin. Commercial epichlorohydrin (Eastman) was redistilled at atmospheric pressure through a 20-in. Vigreux column, and the fraction boiling at 115–116° was collected.

Benzyltrimethylammonium chloride. Commercial preparations, either the crystalline solid (Eastern Chemical Corp.) or the 60–61% aqueous solution (Commercial Solvents Corp.) were used. The solid was hygroscopic and was dried at 110° before use.

Preparation of glycidyl stearate. (a) *Reaction of stearic acid and epichlorohydrin in the presence of benzyltrimethylammonium chloride.* The following detailed procedure illustrates the general method used to prepare crude glycidyl stearate from stearic acid. Variations in this procedure, such as changes in reaction time, reaction temperature, and water content, are listed in Table I together with the results obtained. In those experiments in which added water was present in the reaction mixture, the addition of water was made either prior to or simultaneously with the addition of catalyst.

A mixture of epichlorohydrin (74.0 g., 0.8 mole) and stearic acid (28.4 g., 0.1 mole) was heated to 110°, and solid benzyltrimethylammonium chloride (0.5 g., 0.0027 mole) was added in one batch. The mixture was heated at reflux for 30 min. (at which time there was no remaining acidity), was cooled to 60°, and was washed twice with water (50 ml.) at 45–50° for 30 min. each time. The wash waters were discarded, and unchanged epichlorohydrin was removed from the organic phase by distillation under nitrogen and at reduced pressure until the temperature of the residue reached 70° at 7 mm. Toluene (50 ml.) was added to the residue, and remaining epichlorohydrin was removed as the toluene azeotrope by distillation until the temperature of the residue again reached 70° at 7 mm. The distillation with toluene was repeated. The final residue was crude glycidyl stearate (37.5 g.; oxirane oxygen, 3.0%) (theory for glycidyl stearate, 4.7%). The hydrobromic-acetic acid method of Durbetaki[21] was used in all oxirane determinations.

The above crude material, recrystallized from acetone at 3°, gave partly purified glycidyl stearate (oxirane oxygen, 3.7%; Cl, 1.37%, sap. no. 180.3).

The experimental saponification numbers reported in this paper were obtained by saponifying the sample in refluxing alcoholic potassium hydroxide for 5 hr., a period sufficient to achieve quantitative hydrolysis of chlorine atoms. The reported values, therefore, reflect the alkali consumption due to hydrolysis of ester groups as well as that due to hydrolysis of chlorine atoms. Since the impurities are mainly "chlorohydrin esters," the experimental saponification numbers of impure glycidyl esters are considerably higher than the theoretical values for these esters.

(b) *Reaction of sodium stearate and epichlorohydrin in the presence of benzyltrimethylammonium chloride:* (1) To a vigorously agitated suspension of sodium stearate (45.9 g., 0.15 mole) in epichlorohydrin (222.0 g., 2.4 mole) at reflux was added crystalline benzyltrimethylammonium chloride (2.8 g., 0.015 mole) and agitation and heating at reflux were continued for 10 min. The suspension was then cooled to 60° water (125 ml.) was added, and the resulting mixture was agitated vigorously at 45–50° for 45 min. At the end of this period, a small amount of solid, unchanged sodium stearate (A), was removed by filtration, the two layers of the filtrate were separated, and the epichlorohydrin phase was again washed with water (125 ml.). Solid (A) was washed twice with hot acetone, and the latter was added to the epichlorohydrin solution. (A) after drying weighed 0.4 g. Unchanged epichlorohydrin was removed from the organic phase by distillation under nitrogen and at reduced pressure, finally with toluene, as described above. Residue: crude glycidyl stearate (50.2 g.; oxirane oxygen, 4.25%; sap. no. 171.3; Cl, 0.4%).

Variations in the above procedure included changes in reaction time, reaction temperature, and water content and are listed in Table II together with the results obtained.

An alternate procedure, used for larger scale preparations, follows: (2) Sodium stearate (367.2 g., 1.2 moles), epichlorohydrin (1776 g., 19.2 moles), and benzyltrimethylammonium chloride (22.3 g., 0.12 mole) were combined as before and allowed to reflux for 30 min. The reaction mixture was cooled, washed twice with water (720 ml. each time), and the washed epichlorohydrin solution was cooled at 0° and filtered. The cake was washed with cold methanol (400 ml.) and allowed to air-dry. Crude glycidyl stearate (probably still containing some epichlorohydrin) (358 g.; oxirane oxygen, 4.40%). The crude material (345 g.) was dissolved in methyl acetate (3450 g.), treated with Florisil[22] (30 g.) for 45 min. with occasional stirring, filtered, and cooled at 2°. Filtration, washing of the cake with cold methyl acetate (520 g.), and airdrying of the cake gave glycidyl stearate (297 g.; oxirane oxygen, 4.48%, equivalent to 95.4% glycidyl stearate).

(c) *Preparation of refined glycidyl stearate.* Crude glycidyl stearate (oxirane oxygen, 3.76%) prepared from stearic acid, recrystallized four times from methyl acetate at 2° (oxirane content did not change after first recrystallization), gave refined glycidyl stearate (oxirane oxygen, 4.49%).

(21) A. J. Durbetaki, *Anal. Chem.*, **28**, 2000 (1956).

(22) Reference to commercial products does not imply endorsement by the United States Department of Agriculture over similar products not mentioned.

The latter product, recrystallized from acetone, gave glycidyl stearate (oxirane oxygen, 4.49%; m.p. 51.9–52.7°; sap. no. 165.3; total active hydrogen (Zerewitinoff), 0.015%; Cl, 0.09%).

Anal. Calcd. for $C_{21}H_{40}O_3$: C, 74.06; H, 11.84; O (total), 14.10. Found: C, 74.16; H, 12.03; O (total), 14.15.

Elemental analysis, saponification number, chlorine, and active hydrogen content indicated that the purity of the above material was in excess of 99%, but according to the oxirane determination, it was only 95.7% pure. It is suspected that the analytical method for oxirane gives somewhat low results, and that the actual purity of the refined product exceeded 99%.

In addition to methanol and methyl acetate, dimethylformamide, acetone, petroleum ether (b.p. 63–70°), nitromethane and acetonitrile may be used as solvents in the crystallization of glycidyl stearate. In most of these, however, the solubilities of glycidyl stearate and the corresponding "chlorohydrin ester" (I and II) are too similar to permit effective separation.

Crude materials of low glycidyl stearate content (and correspondingly high content of "chlorohydrin ester") are difficult to purify by any of the methods attempted. Distillation at reduced pressure gave some enrichment of glycidyl stearate content but had to be carried out rapidly to avoid extensive losses, probably because of interaction of the desired product with hydroxyl groups of the impuri ies at elevated temperatures. Treatment of the crude material with phenyl isocyanate to tie up hydroxyl groups also resulted in significant losses of epoxy function, possibly because of interaction of the phenylurethans formed with the oxirane group.

Preparation of diglycidyl azelate. (a) *Reaction of azelaic acid and epichlorohydrin in the presence of benzyltrimethylammonium chloride.* Azelaic acid (28.2 g., 0.15 mole) and epichlorohydrin (222.0 g., 2.4 moles) were heated to 115° and benzyltrimethylammonium chloride (5.78 g., 0.03 mole) was added to the clear solution. The reaction mixture, after 30 min. at reflux, did not contain any unchanged acid (acid number = 0) and was cooled to 60°. Vigorous agitation with water (150 ml.) for 1 hr., to extract the catalyst, was followed by distillative removal of epichlorohydrin in the usual manner. The liquid residue was then heated further at 0.09 mm. and 60–90° under nitrogen, causing distillation of a clear liquid (B). The resulting residue was crude diglycidyl azelate ($n_D^{35.5}$ 1.4669; oxirane oxygen, 6.18%) (calcd. for diglycidyl azelate: 10.63%). Two recrystallizations of the crude material from 95% ethanol at −25° gave impure diglycidyl azelate ($n_D^{35.5}$ 1.4597; oxirane oxygen, 8.44%). Attempted resolution of the residue by chromatography using a Florisil column and benzene-petroleum ether (b.p. 63–70°) as eluent gave a maximum oxirane oxygen content of 8.82% in one fraction with poor resolution. Use of neutral alumina instead of Florisil resulted in almost complete destruction of the oxirane ring.

Distillate B (7.3 g.; $n_D^{35.5}$ 1.4742) was identified as impure glycerol α-dichlorohydrin from its infrared spectrum and from the prepared phenylurethan.

(b) *Reaction of disodium azelate and epichlorohydrin in the presence of benzyltrimethylammonium chloride (nonaqueous medium).* A suspension of disodium azelate (17.4 g., 0.075 mole) in epichlorohydrin (222.0 g., 2.4 moles) was heated to reflux with stirring, and solid benzyltrimethylammonium chloride (3.8 g., 0.02 mole) was added. The mixture was agitated at gentle reflux (116–119.5°) for 6 hr., cooled to 90°, washed twice with water (150-ml. portions), and worked up, as described for glycidyl stearate, by distillative removal of free epichlorohydrin at reduced pressure. The liquid distillation residue was crude diglycidyl azelate (33.3 g.; oxirane oxygen 6.95%). The weight and oxirane content indicate a conversion of 96.5% of the carboxylate groups to glycidyl ester, based on the assumption that the oxirane content is due solely to glycidyl ester groups. This assumption is not warranted in this case, however, since prolonged contact of refluxing epichlorohydrin with benzyltrimethylammonium chloride gives rise to oxirane containing materials which remain with the distillation residue (see below, Reaction of Epichlorohydrin and Benzyltrimethylammonium Chloride). The calculated conversion of carboxylic groups to glycidyl ester is 77.8%, after correction for the amount of oxirane-containing nonester impurities estimated to be present.

(c) *Reaction of aqueous disodium azelate and epichlorohydrin in the presence of benzyldimethylammonium chloride.* Epichlorohydrin (400 g., 4.3 moles was heated to reflux in a three-neck flask equipped with two addition funnels, stirrer, and Dean-Stark water trap topped by a reflux condenser. Solid benzyltrimethylammonium chloride (11.6 g., 0.06 mole) was added in one batch. Epichlorohydrin (100 g., 1.1 moles) was allowed to run into the boiling mixture from one of the addition funnels at a rate sufficient to keep the amount of epichlorohydrin in the reaction mixture approximately constant. A solution of disodium azelate (69.6 g., 0.3 mole) in water (140 ml.) was preheated to 80–90° and maintained at that temperature by means of a heat lamp, while it was added dropwise to the boiling reaction mixture. Water and epichlorohydrin distilling out of the mixture were collected in the Dean-Stark tube, cooled to room temperature in a separatory funnel, the phases separated, and the epichlorohydrin phase returned to the proper addition funnel.[23]

Upon completion of azelate addition (35 min.), distillation of water and epichlorohydrin as well as epichlorohydrin recycling were continued for 15 min. A total of 455 ml. of epichlorohydrin and 133 ml. of water were distilled. The reaction mixture was cooled and was washed with two portions of water (200 ml. each). Acidification of the combined wash waters did not result in the formation of a precipitate, showing that sodium azelate had been consumed completely. The epichlorohydrin solution was worked up in the usual manner by distillative removal of epichlorohydrin at reduced pressure under nitrogen. The liquid residue was crude diglycidyl azelate (90.8 g.; oxirane oxygen, 8.13%; $n_D^{35.5}$ 1.4613; sap. no. 409.3; Cl, 3.90%).

(c) *Preparation of refined diglycidyl azelate.* Crude diglycidyl azelate (80.6 g., oxirane oxygen, 8.13%) was dissolved in 500 ml. of a 1:1 solution of benzene and petroleum ether (b.p. 63–70°), Florisil (8.0 g.) was added, and the mixture was allowed to stand for 1 hr. with occasional agitation. The mixture was then filtered and the filtrate was distilled at atmospheric pressure to obtain a liquid residue which was further heated at 50–65° and 2 mm. pressure for 30 min. The remaining liquid was partially purified diglycidyl azelate (70.3 g.; oxirane oxygen, 8.39%). The latter material was recrystallized three times from aqueous methanol (9 volumes methanol plus 1 volume water) at −25° to obtain refined diglycidyl azelate [oxirane oxygen, 10.33%, (theory, 10.63%), $n_D^{35.5}$ 1.4573; sap. no. 375.0; (theory, 373.0), Cl, 0.09%; active hydrogen (Zerewitinoff), 0.075%]. Other methods of purification were tried, especially on some of the crude materials of low purity. Column chromatography on Florisil using benzene–petroleum ether (b.p. 63–70°) mixtures as eluent gave considerable improvement in purity but very poor resolution. Alumina used as adsorbant destroyed the oxirane group completely, perhaps by isomerization analogous to reactions of other epoxy compounds at high temperatures.[24] Crystallization from solvents other than aqueous methanol or 95% ethanol proved unsatisfactory. Distillation gave poor separation and, at higher pot temperatures, led to large losses by polymerization. Attempted extraction of diglycidyl azelate from the crude ester mixture with benzene–petroleum ether (b.p.

(23) In later experiments, use of a modified trap permitted continuous return of distilled epichlorohydrin to the reaction mixture.

(24) F. G. Ponomarev, *Zhur. Obshcheĭ Khim.*, **24**, 1371 (1954). [*Chem. Abstr.*, **49**, 10850e (1955)].

63–70°) showed some promise but was not explored further.

Reaction of epichlorohydrin and benzyltrimethylammonium chloride. Epichlorohydrin (222.0 g., 2.4 moles) and benzyltrimethylammonium chloride (3.8 g., 0.02 mole) were heated at reflux for 6 hr., and the reaction mixture was cooled and agitated vigorously with water (150 ml.) for 1 hr. Unchanged epichlorohydrin was removed, as previously described, by distillation at reduced pressure under nitrogen. A liquid residue, nonvolatile under these conditions, remained (8.2 g.; oxirane oxygen, 5.6%) (qualitative test for chlorine-positive).

Reaction of hydrogen chloride and glycidyl stearate. To an anhydrous solution of hydrogen chloride in ether (500 ml., hydrogen chloride concentration—0.40*N*), prepared by the method of Swern *et al.*[25] was added a solution of glycidyl stearate (34.0 g; oxirane oxygen, 4.47%) in ether (250 ml.) The resulting solution was allowed to stand at room temperature for 16 hr. and was then washed successively with water, dilute aqueous bicarbonate, and again water until the water washes were neutral to *p*H paper. The ether solution was then distilled on a steam bath and the oily residue (38.6 g.; oxirane oxygen, 0) was allowed to solidify at room temperature. The residue precipitated as a gelatinous solid on recrystallization from aqueous methanol at room temperature. Recrystallization from an ether-petroleum ether (b.p. 30–60°) mixture at −25° gave a crystalline solid which was dried to give "chlorohydrin ester" (presumably a mixture of 3-chloro-2-hydroxypropyl stearate and 2-chloro-3-hydroxypropyl stearate) (n_D^{55} 1.4500).

Anal. Calcd. for $C_{21}H_{41}O_3Cl$: C, 66.90; H, 10.96; Cl, 9.40; OH, 4.51. Found: C, 66.90; H, 10.94; Cl, 9.95; OH, 4.60.

Identification of some by-products in the preparation of glycidyl stearate. (a) *By-products in the reaction of stearic acid and epichlorohydrin.* Stearic acid (142.0 g., 0.5 mole) and epichlorohydrin (370.0 g., 4.0 mole) were heated to 105° and benzyltrimethylammonium chloride (4.1 g., 0.022 mole) was added. The mixture was heated at reflux for 22 min. (no remaining acidity), cooled, and washed twice with water (250 ml.). The epichlorohydrin solution was cooled at 2° overnight and filtered. The filtrate was reserved and the cake slurried twice with methanol (400 ml.) at room temperature, and each time the slurry was cooled at 2° and filtered.

The epichlorohydrin filtrate and the combined methanol filtrates were distilled separately at reduced pressure under nitrogen, and each residue was freed of epichlorohydrin completely by addition of toluene (50-ml. portions) and distillation at reduced pressure. The liquid residues were combined to give mixture (C) (49.6 g.; oxirane oxygen, 0.93%; sap. no., 507; Cl, 27.2%).

Mixture C (32.0 g.) was heated at 40–85° and 0.06–0.07 mm. pressure, and a liquid (D), distilling at 27–30.5° at 0.06 mm., was collected (10.7 g.; $n_D^{35.5}$ 1.4754; oxirane oxygen, 0.21%). D was identified as impure glycerol α-dichlorohydrin from its infrared spectrum and from its phenylurethan (m.p. 72–73°).

The still residue from C, after cooling, was a solid (E). A portion of E was dissolved in warm petroleum ether (b.p. 63–70°), and the solution was allowed to cool to room temperature, giving a second solid which, after two recrystallizations from petroleum ether (b.p. 63–70°) was identified as glycerol monostearate (m.p. 73.5–74.3°).

Anal. Calcd. for $C_{21}H_{42}O_4$: C, 70.34; H, 11.81; OH, 9.48. Found: C, 70.32; H, 11.91; OH, 9.09.

Another portion of E dissolved in petroleum ether (b.p. 63–70°) the cooled mixture filtered, and the filtrate evaporated to dryness gave a solid which was recrystallized from methanol. The infrared spectrum of this solid was identical with that of authentic "chlorohydrin ester" prepared by reaction of hydrogen chloride and the glycidyl stearate.

(b) *By-products in the reaction of sodium stearate and epichlorohydrin.* Sodium stearate (153.0 g., 0.5 mole) and epichlorohydrin (740.0 g., 8.0 mole) were heated to reflux, and benzyltrimethylammonium chloride (9.3 g., 0.05 mole) was added in one batch. The mixture was heated at reflux for 5 min., cooled to 90°, and stirred vigorously with water (500 ml.) for 30 min. The mixture was filtered to remove unchanged sodium stearate (1.5 g.), the phases of the filtrate were separated, and the epichlorohydrin layer was again agitated with water (500 ml.) The washed epichlorohydrin solution was cooled at 2° and filtered. The epichlorohydrin filtrate was reserved, and the cake (144.9 g.) was recrystallized from methanol at 10° to give recrystallized glycidyl stearate (139.1 g.). The methanol mother liquor was distilled at reduced pressure to remove the solvent. The residue, after addition of toluene (50 ml.), was heated to 60° at 15 mm. to remove traces of epichlorohydrin. The resulting solid (2.7 g.) was recrystallized from ether–petroleum ether (b.p. 63–70°) to give a white solid material (oxirane oxygen, 1.58%) which, according to its infrared spectrum, was a mixture of glycidyl stearate and "chlorohydrin ester."

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(25) D. Swern, T. W. Findley, G. N. Billen, and J. T. Scanlan, *Anal. Chem.*, 19, 414 (1947).

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF HOFFMANN-LA ROCHE INC.]

Synthesis of Arachidonic Acid

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Arachidonic acid (eicosa-5,8,11,14-tetraenoic acid) has been synthesized from acetylenic intermediates. The properties of the methyl ester were found to be practically identical with those of the methyl ester of naturally occurring arachidonic acid.

Linoleic acid (I,$x = 4, y = 2, z = 6$), γ-linolenic acid (I,$x = 4, y = 3, z = 3$) and arachidonic acid (I,$x = 4, y = 4, z = 2$) belong to a group known as

$$CH_3(CH_2)_x(CH{=}CH{-}CH_2)_y(CH_2)_zCOOH$$
I

the essential fatty acids (EFA).[1] It is generally accepted that the all *cis* geometric isomers of these unsaturated fatty acids are the biologically active forms.

(1) For comprehensive reviews see (a) *The Vitamins*, W. H. Sebrell, Editor, Academic Press Inc., New York, N. Y., 1954, Vol. II, Chapter 7, pp. 267–319; (b) H. J. Deuel and R. Reiser in *Vitamins and Hormones*, Academic Press Inc., New York, N. Y., 1955, Vol. XIII, pp. 29–70; (c) *Essential Fatty Acids*, H. M. Sinclair, Editor, Academic Press Inc., New York, N. Y., 1958.