Organic Reactions
Vol. 5, Chapter 10
p. 413-440 (1949)

THE DARZENS GLYCIDIC ESTER CONDENSATION

MELVIN S. NEWMAN

The Ohio State University

and

BARNEY J. MAGERLEIN

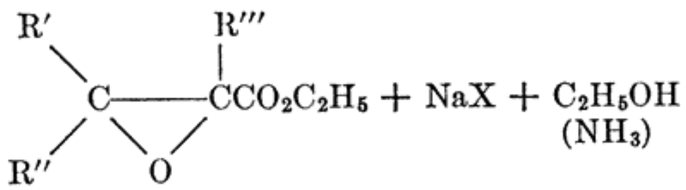
The Upjohn Company

CONTENTS

INTRODUCTION

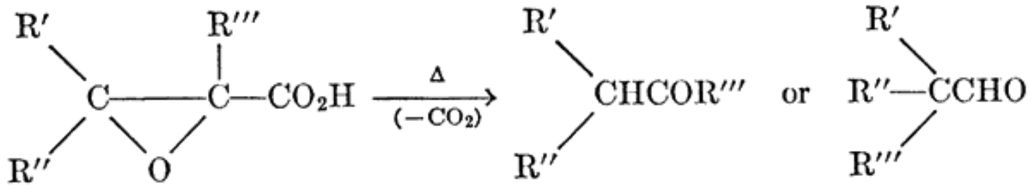
The Darzens glycidic ester condensation involves the condensation of an aldehyde or ketone with an α-halo ester to produce an α,β-epoxy ester (glycidic ester). The most frequently used condensing agents are sodium ethoxide and sodium amide.

$$R'COR'' + R'''CHXCO_2C_2H_5 \xrightarrow[(NaNH_2)]{C_2H_5ONa}$$



$$+ NaX + C_2H_5OH\ (NH_3)$$

The glycidic esters are of interest primarily because they can be converted into aldehydes and ketones having a higher carbon content than the original aldehydes or ketones. This transformation occurs after hydrolysis to and decarboxylation of the epoxy acids and is accompanied by rearrangement when an aldehyde is formed.

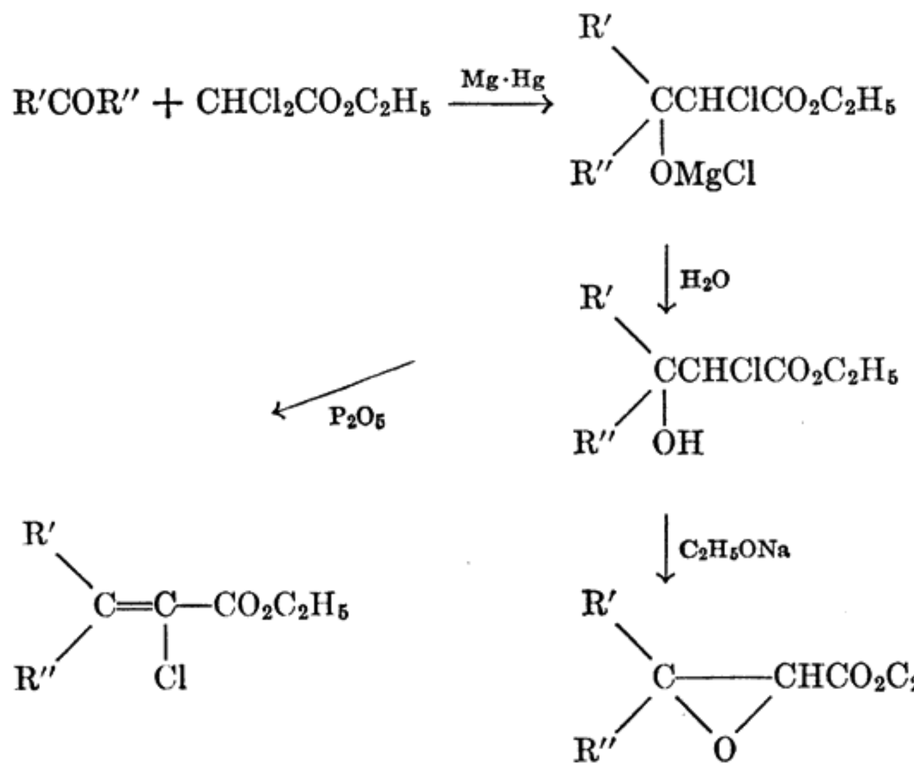


The first synthesis of a glycidic ester was performed by Erlenmeyer,[1] who obtained ethyl β-phenyl-α,β-epoxypropionate by condensing benzaldehyde with ethyl chloroacetate by means of sodium. It remained for Darzens, however, to develop and generalize this reaction.[2-13] He

[1] Erlenmeyer, Jr., *Ann.*, **271**, 161 (1892).
[2] Darzens, *Compt. rend.*, **139**, 1214 (1904).
[3] Darzens, *Compt. rend.*, **141**, 766 (1905).
[4] Darzens, *Compt. rend.*, **142**, 214 (1906).
[5] Darzens and Lefebure, *Compt. rend.*, **142**, 714 (1906).
[6] Darzens, *Compt. rend.*, **144**, 1123 (1907).
[7] Darzens, *Compt. rend.*, **145**, 1342 (1907).
[8] Darzens, *Compt. rend.*, **150**, 1243 (1910).
[9] Darzens and Rost, *Compt. rend.*, **151**, 758 (1910).
[10] Darzens, *Compt. rend.*, **152**, 443 (1911).
[11] Darzens and Sejourné, *Compt. rend.*, **152**, 1105 (1911).
[12] Darzens and Leroux, *Compt. rend.*, **154**, 1812 (1912).
[13] Darzens, *Compt. rend.*, **195**, 884 (1932).

preferred sodium ethoxide as the condensing agent. Shortly after the appearance of Darzens' first paper, Claisen [14] reported that sodium amide could be used as the condensing agent. The glycidic ester condensation has not been applied as widely as one would expect in view of the number and variety of compounds that can be prepared by its use.

Darzens [15,16,17] has described another procedure which involves the reaction of aldehydes and ketones with ethyl dichloroacetate and dilute magnesium amalgam. The first product of this reaction is a β-hydroxy α-chloro ester which is quantitatively converted to a glycidic ester by treatment with sodium ethoxide. Alternatively, the hydroxy chloro esters may be dehydrated to yield α-chloro unsaturated esters.



The mechanism of glycidic ester formation probably involves the addition of the enolate of the halo ester to the carbonyl group of the aldehyde or ketone,* followed by an intramolecular nucleophilic dis-

* Early ideas involving addition of the condensing agent to the carbonyl group of the aldehyde or ketone, Fourneau and Billeter, *Bull. soc. chim. France*, [5] **6**, 1616 (1939), or the conversion of the aldehyde or ketone to its enolate by the base, Rutowski and Dajew, *Ber.*, **64**, 693 (1931), appear inadequate. Scheibler and Tutundzitsch, *Ber.*, **64**, 2916 (1931), first suggested the formation of the enolate of the halo ester, but their detailed mechanism appears unnecessarily complicated.

[14] Claisen, *Ber.*, **38**, 693 (1905).
[15] Darzens, *Compt. rend.*, **151**, 883 (1910).
[16] Darzens, *Compt. rend.*, **203**, 1374 (1936).
[17] Darzens and Lévy, *Compt. rend.*, **204**, 272 (1937).

placement on carbon. The function of the basic condensing agent is to convert the halo ester to its enolate.

$$ClCH_2CO_2C_2H_5 + \underset{(NaNH_2)}{C_2H_5ONa} \rightarrow [ClCHCO_2C_2H_5]^-Na^+ + \underset{(NH_3)}{C_2H_5OH}$$

$$R'COR'' + [ClCHCO_2C_2H_5]^-Na^+ \rightarrow \left[\begin{array}{l} R' \quad O \\ \quad\diagdown\diagup \\ R''\quad C(Cl)CHCO_2C_2H_5 \end{array}\right]^- Na^+$$

$$\rightarrow \begin{array}{l} R' \quad O \\ \quad\diagdown\diagup \\ R''\quad C\text{—}CHCO_2C_2H_5 \end{array} + NaCl$$

Evidence supporting the formation of the enolate of the chloro ester is the fact that about 79% of the theoretical amount of ammonia is evolved on treating a suspension of sodium amide in ether with ethyl chloroacetate.[18,*] It has been shown that the sodium enolates of ketones react with chloro esters to give glycidic esters.[18,19] This result is consistent with the above mechanism if it is postulated that the enolate of the ketone reacts with the chloro ester to convert it to its enolate.

$$\begin{array}{l} ONa \\ | \\ CH_3C{=}CH_2 \end{array} + ClCH_2CO_2C_2H_5 \rightarrow CH_3COCH_3 + [ClCHCO_2C_2H_5]^-Na^+$$

SCOPE AND LIMITATIONS

Carbonyl Components

Of the many types of aldehydes and ketones from which the desired condensation products have been isolated, only formaldehyde,[4] monosubstituted acetaldehydes,[4] and a few terpene ketones, such as carvone and pulegone,[4] give generally poor yields. Aromatic aldehydes containing alkyl, alkoxy, methylenedioxy, and chloro groups give fair to good yields. Although no study of the effect of steric hindrance has been made, 2,4,6-trimethylbenzaldehyde is reported to give the expected product,[20] but in unstated yield. Aliphatic ketones, including methyl ketones, α,β-unsaturated ketones, and cyclic ketones, react smoothly.

* The hypothesis that a halo ester may form an enolate is supported by the observation that chloromalonic ester may be alkylated to form benzylchloromalonic ester by treatment with sodium ethoxide followed by benzyl chloride, Conrad, *Ann.*, **209**, 241 (1881).

[18] Unpublished experiments by Newman and Magerlein at the Ohio State University.

[19] Rutowski and Dajew, *Ber.*, **64**, 693 (1931).

[20] Chuit and Bolle, *Bull. soc. chim. France*, [4] **35**, 200 (1924).

The successful use of a Mannich base, 2-dimethylaminocyclohexanone, has been reported,[21] but the analogous 4-dimethylamino-2-butanone failed to give the expected ester.[21] Aromatic and aromatic-aliphatic ketones give very satisfactory yields. The presence of a nuclear chlorine atom appears to improve the yield somewhat.[18] Although a fairly representative group of aldehydes and ketones has been investigated, no systematic study of the effect of the structure of the carbonyl component on the yield of glycidic ester has been reported.

Halogenated Esters

As a rule, chloro esters are preferable to bromo or iodo esters although bromo esters have been used successfully. With cyclohexanone, it has been shown that the *p*-toluenesulfonate of ethyl glycolate may be substituted for the chloro ester.[22] With ethyl chloroacetate, isobutyrophenone yields the glycidic ester, whereas with ethyl iodoacetate it yields an alkylation product, ethyl β,β-dimethyl-β-benzoylpropionate; with ethyl bromoacetate a mixture of the two products results.[23]

$$C_6H_5COCH(CH_3)_2 \begin{cases} \xrightarrow{ClCH_2CO_2C_2H_5} \begin{array}{l} (CH_3)_2CH \quad O \\ \quad\diagdown\diagup \\ C_6H_5\quad C\text{—}CHCO_2C_2H_5 \end{array} \quad \text{(A)} \\ \xrightarrow{BrCH_2CO_2C_2H_5} \text{Mixture of A and B} \\ \xrightarrow{ICH_2CO_2C_2H_5} C_6H_5COC(CH_3)_2CH_2CO_2C_2H_5 \quad \text{(B)} \end{cases}$$

Very little is known of the condensation of halo esters other than halo acetates, halo propionates, and halo butyrates, ethyl α-chlorolaurate being the only example of a higher ester described.[13]

The effect of the alkyl group of the halo ester on reactivity or yield has not been investigated to any extent. If sodium amide is the condensing agent, the ethyl ester is preferable to the methyl ester because of increased formation of chloroacetamide with the methyl ester.[14] In experiments involving acetone, benzaldehyde, acetophenone, and cyclohexanone the following alkyl chloroacetates and chloropropionates gave yields comparable to those obtained with methyl and ethyl esters: [18]

[21] Howton, *J. Org. Chem.*, **12**, 379 (1947).

[22] Newman and Magerlein, *J. Am. Chem. Soc.*, **69**, 469 (1947).

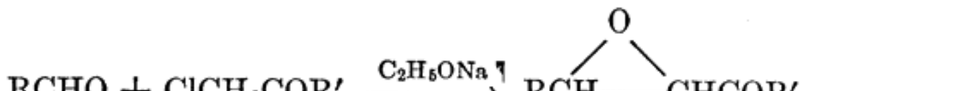
[23] Haller and Ramart-Lucas, *Compt. rend.*, **159**, 143 (1914); Ger. pat. 586,645 [*Frdl.*, **20**, 781 (1935)].

propyl and isopropyl, allyl, cyclohexyl, *n*-amyl, benzyl, and 2-ethylhexyl; with β-methallyl and tetrahydrofurfuryl esters the yields were lower. There is some evidence that better yields of condensation products may be obtained with halo amides. An 80% yield of glycide amide is obtained from acetone and the diethylamide of chloroacetic acid [24] whereas with ethyl chloroacetate [2,14,19] much lower yields result. However, it has not been shown that the glycidic amides can be hydrolyzed and decarboxylated to give aldehydes or ketones in improved yields.

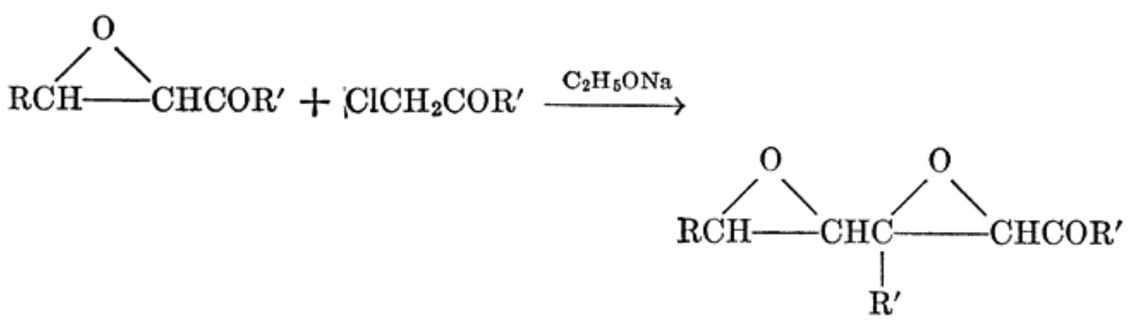
More complex halo esters, such as ethyl β-hydroxy-α-chloropropionate,[25] ethyl α,β-dichloropropionate,[25] and ethyl α-bromo-β,β-diethoxypropionate,[26] have failed to undergo the glycidic ester condensation.

Other Halogenated Compounds

Certain other halogenated compounds have been used in place of halo esters. α-Halo ketones have been condensed with a variety of aldehydes to yield α,β-epoxyketones.[27-31]



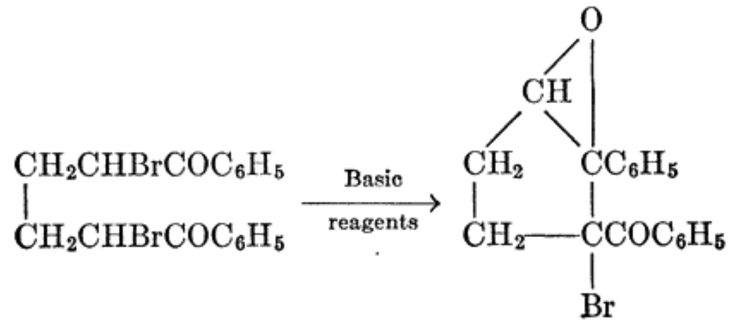
These epoxyketones may condense with a second molecule of halo ketone to yield α,β,γ,δ-diepoxyketones.[28a]

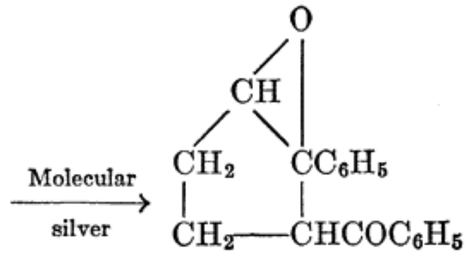


When 1,4-dibromo-1,4-dibenzoylbutane is treated with sodium cyanide,[32] diethylamine,[32] sodium acetate,[32] or the sodium derivative

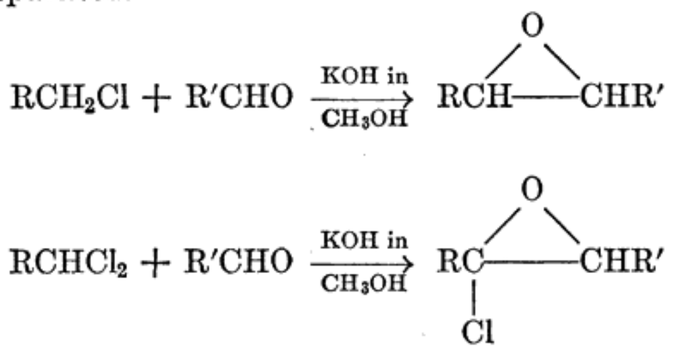
[24] von Schickh, *Ber.*, **69**, 971 (1936).
[25] Yarnall and Wallis, *J. Org. Chem.*, **4**, 284 (1939).
[26] Oroshnik and Spoerri, *J. Am. Chem. Soc.*, **67**, 721 (1945).
[27] Widman, (*a*) *Ann.*, **400**, 86 (1913); (*b*) *Ber.*, **49**, 477 (1916).
[28] Bodforss, (*a*) *Ber.*, **49**, 2795 (1916); (*b*) *Ber.*, **51**, 192 (1918); (*c*) *Ber.*, **52**, 142 (1919).
[29] Jörlander, (*a*) *Ber.*, **49**, 2782 (1916); (*b*) *Ber.*, **50**, 406, 1457 (1917).
[30] Freudenberg and Stoll, *Ann.*, **440**, 41 (1924).
[31] Murakami and Irie, *Proc. Imp. Acad.* (*Tokyo*), **10**, 568 (1934) [*C.A.*, **29**, 1818 (1935)].
[32] Kao and Fuson, *J. Am. Chem. Soc.*, **54**, 313 (1932).

of malonic ester [33] a cyclic epoxyketone is produced; with molecular silver the debrominated analog is obtained.[33]





A number of substituted halides of the benzyl [34,35,36] and benzal [34b] types has been condensed with aldehydes and ketones to give epoxy and α-haloepoxy compounds in yields which, although usually not stated, were often good. Stereoisomeric forms of the epoxy compounds were occasionally separated.



The aldehydes used include benzaldehyde, *o*-, *m*-, and *p*-nitrobenzaldehyde, *p*-methoxybenzaldehyde, diphenylacetaldehyde, cinnamaldehyde, and furfural; the ketones were fluorenone and 2,7-dibromofluorenone. As halides, *o*- and *p*-nitrobenzyl chloride, 9-chlorofluorene, and 9-bromo-10-anthrone were used.

[33] Kao, *J. Am. Chem. Soc.*, **62**, 356 (1940).
[34] (*a*) Hatzig, Inaugural dissertation, Strasbourg, 1909; (*b*) Barrow, Inaugural dissertation, Strasbourg, 1909; (*c*) Chrzescinski, Inaugural dissertation, Strasbourg, 1911.
[35] Kleucker, *Ber.*, **55**, 1634 (1922).
[36] Bergmann and Hervey, *Ber.*, **62**, 902 (1929).

Side Reactions

Few investigators have studied the non-glycidic-ester portion of the reaction products. Some unchanged ketone may usually be recovered. Possible contaminants of the glycidic esters are the isomeric oxygen or carbon alkylation products formed by alkylation of the enolate of the ketone by the halo ester. The boiling ranges reported for the glycidic esters usually cover 5–10°, so that such contamination is entirely possible. The condensation product from β-ionone and ethyl chloroacetate is considered to be a mixture of three isomeric products: glycidic ester; α-keto ester; and the enolic form of the latter.[37] Halogen in the condensation products indicates the presence of an α-halogen α,β-unsaturated ester.[14] High-boiling products, including resinous material, are frequently noted. These may result from self-condensation of the aldehyde or ketone [38] or of the halo ester; ethyl chloroacetate in ether reacts with sodium to yield an ethoxy chloro acetoacetate of undetermined structure.[39] Vacuum distillation of high-boiling glycidic esters should be done at as low a temperature as possible in order to guard against rearrangement to an α-keto ester.[40, 41, 42]

SELECTION OF EXPERIMENTAL CONDITIONS

The reactions are carried out under strictly anhydrous conditions preferably in an inert atmosphere. Often no solvent is used, care being taken to prevent undue temperature rise when the condensing agent is added. It seems best to add the condensing agent to a mixture of the reaction components, of which the halo ester is preferably in some excess.[37] It has been found [18] advantageous to use 1.6 moles of chloro ester and 1.6 moles of alkoxide to 1 mole of ketone. During the first stage of the reaction it is well to keep the mixture cold, temperatures as low as −80° being recommended.[43] However, in a few cases no reaction occurs at −80°, and a temperature of 0° appears to be preferable.[18] After reaction periods ranging from a few hours to a few days, the mixture is usually heated for an hour on a steam bath. The reaction mixture is then treated with dilute acid and the organic products are generally

[37] Milas, Lee, Sakal, Wohlens, MacDonald, Grossi, and Wright, *J. Am. Chem. Soc.*, **70**, 1584 (1948).
[38] Weidlich and Daniels, *Ber.*, **72**, 1596 (1939).
[39] Fittig and Erlenbach, *Ann.*, **269**, 15 (1892).
[40] Troell, *Ber.*, **61**, 2498 (1928).
[41] Kohler, Richtmyer, and Hester, *J. Am. Chem. Soc.*, **53**, 211 (1931).
[42] Pointet, *Compt. rend.*, **148**, 417 (1909).
[43] Yarnall and Wallis, *J. Org. Chem.*, **4**, 270 (1939).

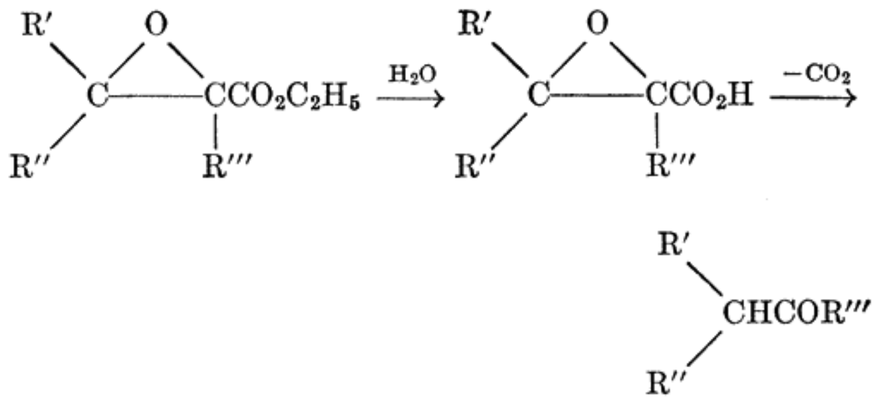
separated by vacuum distillation. At least one glycidic ester rearranged into an α-keto ester at the high temperature needed for vacuum distillation,[40, 41, 42] but this rearrangement seems not to be general.

The most frequently used condensing agents are sodium ethoxide and sodium amide. Of these, sodium ethoxide is the reagent of choice in the few reactions where both have been employed.[18, 37, 40, 44, 45] The use of powdered sodium in various solvents seems to be promising.[46] The sodium ketyl prepared from benzophenone has been used with fair success in one reaction.[19]

The effect of solvent on the yields of glycidic esters has not been extensively investigated. Better yields were obtained in the condensation of cyclohexanone with ethyl α-chloropropionate without solvent than with ether, benzene, or benzene-petroleum ether.[25] A variety of inert solvents has been used, but the experiments do not permit a conclusion concerning the importance of the solvent. Aromatic hydrocarbons have been recommended as solvents in preparations carried out with the aid of metallic sodium; in the presence of such solvents the sodium chloride formed in the reaction separates in a colloidal suspension and does not coat the sodium.[46]

CONVERSION OF GLYCIDIC ESTERS INTO ALDEHYDES AND KETONES

Hydrolysis of glycidic esters to and decarboxylation of the resulting glycidic acids usually yield ketones or aldehydes. R′ and R″ may



represent hydrogen or alkyl or aryl groups, or may be joined in a ring. If R‴ is hydrogen an aldehyde always results; if a methyl group, methyl ketones are formed. The effect of other groups in the R‴ position has

[44] Linstead and Mann, *J. Chem. Soc.*, **1930**, 2070.
[45] Kayser, *Ann. chim.*, [11] **6**, 170 (1936).
[46] Knorr, Laage, and Weissenborn, Ger. pat. 591,452 [*C.A.*, **28**, 2367 (1934)], U. S. pat. 1,899,340 [*C.A.*, **27**, 2962 (1933)].

received little attention: when R‴ is ethyl, an ethyl ketone is obtained;[47] when R‴ is *n*-decyl, an aldehyde results.[13]

The conversion of glycidic esters to acids may be effected by the usual alkaline hydrolysis. A special hydrolysis[14] involves treatment of the ester with one equivalent of sodium ethoxide in absolute ethanol followed by addition of exactly one equivalent of water; addition of dry ether then causes the precipitation of the sodium salt of the glycidic acid.

For the most part, the glycidic acids are converted into the aldehydes or ketones by heating to the decomposition point. Better yields of methyl cyclohexyl ketone may be obtained from α-methyl-α,β-epoxycyclohexylideneacetic acid by two modifications of the above treatment (which gives a 41% yield).[43] In one, the sodium salt of the glycidic acid is heated with sodium hydroxide at 300° (yield 45–56%); in the other, the glycidic acid is treated with dry hydrogen chloride, and the crude chloro hydroxy acid thus obtained is then heated with semicarbazide hydrochloride in pyridine (yield 75%).

The optimum conditions for pyrolysis of the glycidic acid derived from the condensation of β-ionone and ethyl chloroacetate involve heating in pyridine at 130–135° for one to two hours.[37] When this same glycidic acid is decarboxylated by heating in the presence or absence of powdered glass or by passage in the vapor phase under reduced pressure over freshly reduced copper on pumice at 140–160°, products having slightly different properties from those of the product obtained by the pyridine method are obtained.[37] Another group of workers recommends heating in the presence of a small amount of copper powder as the best method for decarboxylating and rearranging this same glycidic acid and the isomeric acid obtained from α-ionone and ethyl chloroacetate,[47a] while a third group of workers reports that no special decarboxylation procedure is necessary for the glycidic ester from β-ionone and ethyl chloroacetate: the glycidic ester is hydrolyzed with cold methanolic sodium hydroxide, the product is extracted in the usual way with ether, and the aldehyde is obtained by vacuum distillation.[47b]

A systematic study of the best conditions for the conversion of glycidic esters to aldehydes or ketones is obviously to be desired, and such a study would contribute much to the wider synthetic use of glycidic esters.

[47] Mousseron and Granger, *Compt. rend.*, **218**, 358 (1944); Mousseron, Winternitz, Granger, Claret, Trinquier, and Combes, *Bull. soc. chim. France*, **1947**, 598.

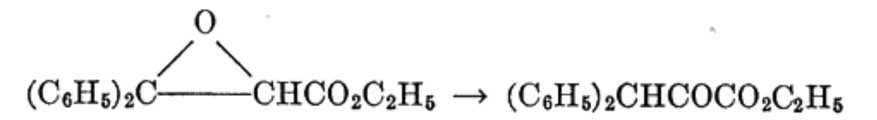
[47a] Heilbron, Johnson, Jones, and Spinks, *J. Chem. Soc.*, **1942**, 727.

[47b] Isler, Huber, Ronco, and Kofler, *Helv. Chim. Acta*, **30**, 1911 (1947).

REACTIONS OF GLYCIDIC ESTERS

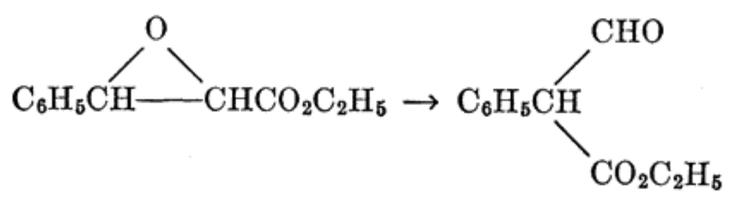
In addition to their conversion to aldehydes and ketones, discussed in the preceding section, the glycidic esters undergo a number of other reactions which should prove to be valuable in synthetic work. In the paragraphs which follow, examples of these reactions are given. No attempt has been made to list all the examples of any one reaction, but it is believed that all the types of reactions are included.

Rearrangement to α- or β-Keto Esters. It has already been pointed out (pp. 420 and 421) that a glycidic ester on heating to a high temperature may undergo rearrangement to a keto ester. Ethyl β,β-diphenylglycidate is isomerized to ethyl β,β-diphenyl-α-ketopropionate on distillation.[40,41,42]



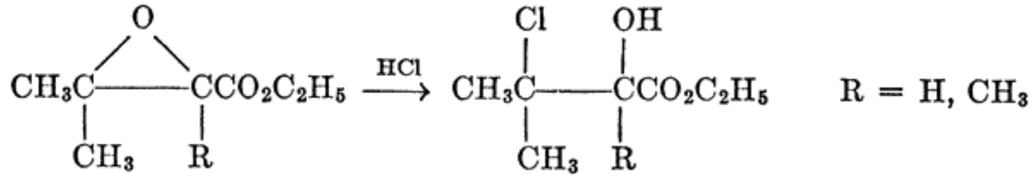
$$(C_6H_5)_2C\!\!-\!\!O\!\!-\!\!CHCO_2C_2H_5 \rightarrow (C_6H_5)_2CHCOCO_2C_2H_5$$

Ethyl β-phenylglycidate, on passage in the vapor state over infusorial earth at 310°, yields the ester of phenylmalonaldehydic acid.[48]



$$C_6H_5CH\!\!-\!\!O\!\!-\!\!CHCO_2C_2H_5 \rightarrow C_6H_5CH(CHO)CO_2C_2H_5$$

Reactions with Hydrogen Halides. The addition of hydrogen chloride in dry ether in the cold to ethyl β,β-dimethylglycidate and to ethyl α,β,β-trimethylglycidate results in the formation of α-hydroxy β-chloro esters.[8] This reaction complements the addition of hypochlorous acid to the corresponding substituted acrylates which yields the isomeric α-chloro β-hydroxy esters.



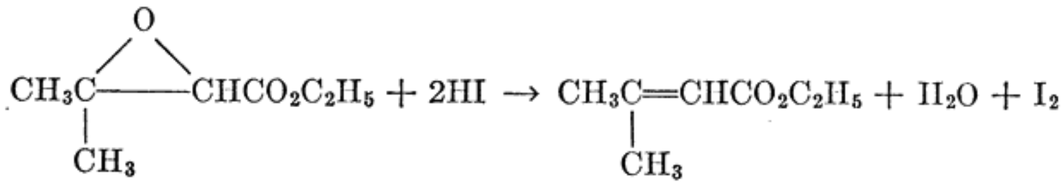
$$CH_3C(CH_3)(R)\!\!-\!\!O\!\!-\!\!CCO_2C_2H_5 \xrightarrow{HCl} CH_3C(CH_3)(R)CCO_2C_2H_5 \qquad R = H, CH_3$$

Hydrogen bromide reacts similarly,[8] but hydrogen iodide yields the acrylate.[8] This latter reaction constitutes another * method for pre-

* A summary of the methods of preparing α,β-unsaturated acids by condensation methods is given in the chapter on the Perkin reaction by J. R. Johnson in *Organic Reactions*, Vol. I, p. 233, John Wiley & Sons, New York, 1942.

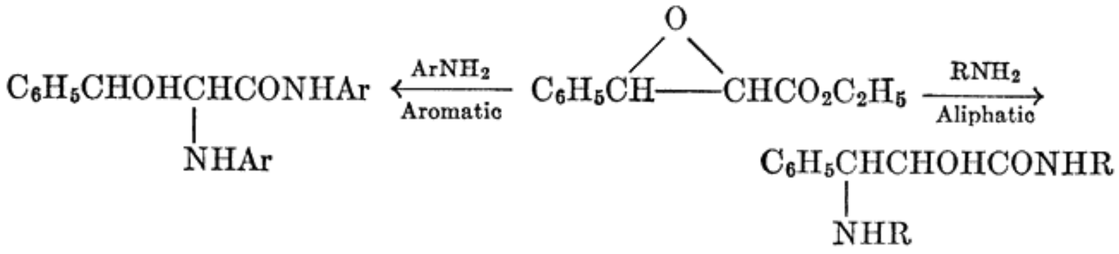
[48] Tiffeneau and Levy, *Anales soc. quím. argentina*, **16**, 144 (1928) [*C.A.*, **24**, 2450 (1930)].

paring α,β-unsaturated esters and might be developed into a procedure

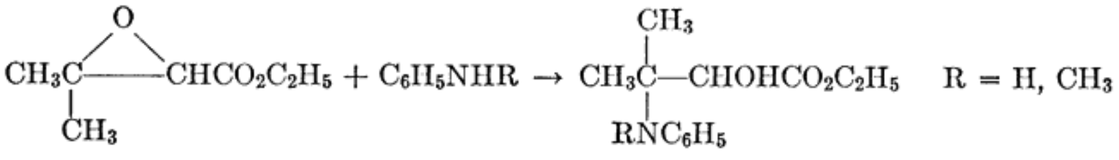


for the quantitative determination of glycidic esters.

Reactions with Ammonia and Amines. Depending upon the reaction conditions, glycidic esters may yield either glycidic amides, hydroxy amino esters, or hydroxy amino amides on treatment with ammonia or amines. The orientation of the hydroxy amino amides appears in doubt. If ammonia or an aliphatic amine is used it is claimed that α-hydroxy β-amino amides are obtained, whereas with an aromatic amine the reverse orientation results.[49]

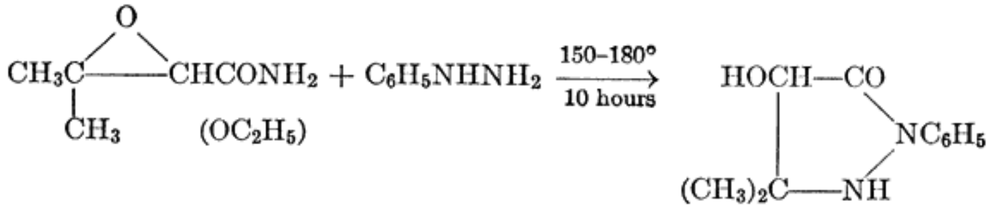


It is stated that with ethyl β,β-dimethylglycidate and aniline or methylaniline an α-anilino-β-hydroxy ester is produced,[24] whereas in a patent the reverse orientation is claimed.[50]



It appears that more work is required before assignment of structure of such amino hydroxy compounds can safely be made by analogy.

With phenylhydrazine, the amide [24] or ethyl ester [51] of β,β-dimethylglycidic acid yields 1-phenyl-3,3-dimethyl-4-hydroxy-5-pyrazolidone.

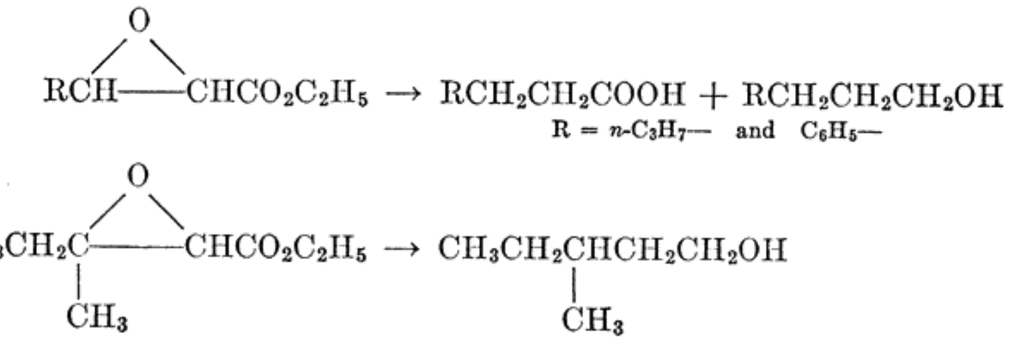


[49] (*a*) Fourneau and Billeter, *Bull. soc. chim. France*, [5] **6**, 1616 (1939); (*b*) [5] **7**, 593 (1940); (*c*) Fourneau and Maréchal, *ibid.*, [5] **12**, 990 (1945).

[50] Schickh, Ger. pat. 583,243 [*C.A.*, **28**, 260 (1934)].

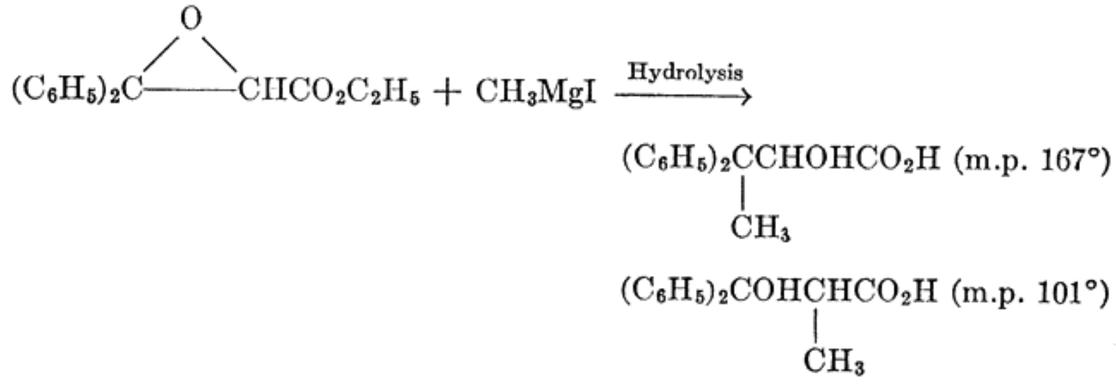
[51] Schickh, Ger. pat. 588,045 [*C.A.*, **28**, 1360 (1934)].

Reduction. The reduction of glycidic esters by heating in alcohols with sodium is said to yield mixtures of the saturated acid and of the corresponding primary alcohol. No details of the experimental procedure or yields are reported.[52] By a similar reduction, β,β-diphenyl-



glycidic ester is reported to yield β,β-diphenyl-α-hydroxypropionic acid.[53] However, in view of the previously mentioned rearrangement of this glycidic ester to form a keto ester on vacuum distillation,[40,41,42] it is possible that the reduction was carried out on the rearranged product.

Grignard Reaction. The product resulting from the action of methylmagnesium iodide on ethyl β,β-diphenylglycidate [54] followed by hydrolysis is claimed to be β,β-diphenyl-α-hydroxybutyric acid. However, the proof of structure consisted in establishing the non-identity of the reaction product (m.p. 167°) with β,β-diphenyl-β-hydroxy-α-methylpropionic acid (m.p. 101°). The alternative possibility, β,β-diphenyl-α-hydroxy-α-methylpropionic acid, was not ruled out. This latter product would be formed if the glycidic ester rearranged to the α-keto ester.



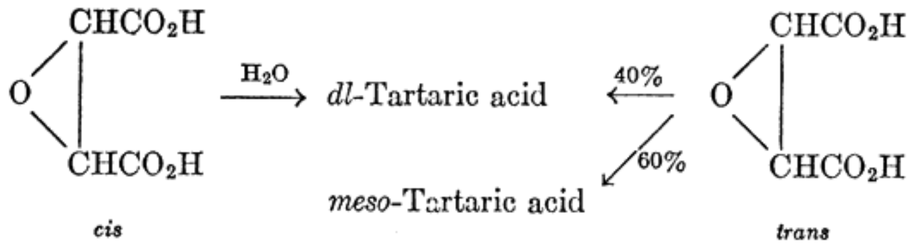
Hydration. Hydration of the *cis* form of ethylene oxide dicarboxylic acid yields *dl*-tartaric acid, whereas the *trans* form yields a mixture of about 40% *dl*-tartaric and 60% *meso*-tartaric acid.[55]

[52] Verley, *Bull. soc. chim. France*, [4] **35**, 487 (1924).

[53] Billon-Bardon, *Compt. rend.*, **188**, 1412 (1929).

[54] Bardon and Ramart, *Compt. rend.*, **183**, 214 (1926).

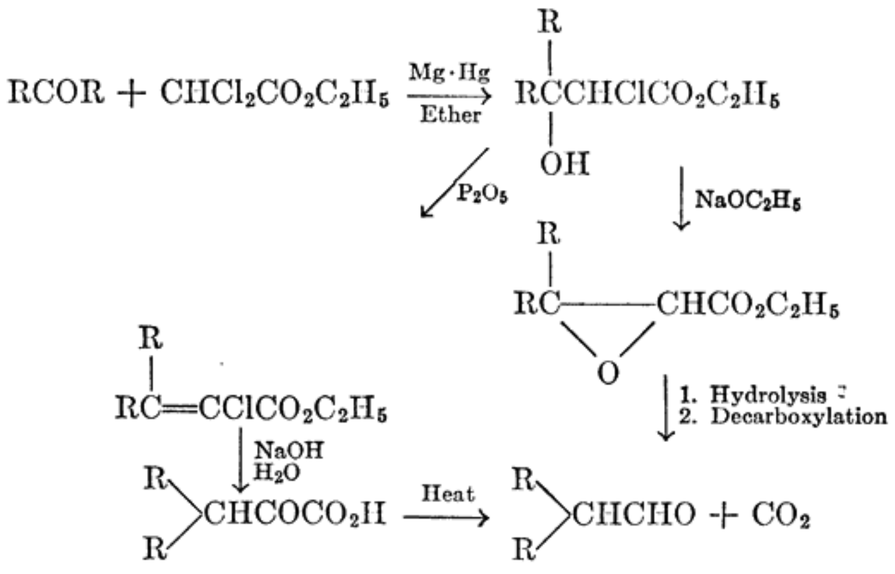
[55] Kuhn and Ebel, *Ber.*, **58**, 919 (1925).



Reaction with Active Methylene Groups. Although details and proof of structure are not given, it is stated that β,β-dimethylglycidic ester and β-phenylglycidic ester react with sodioacetoacetic ester and sodiomalonic ester, respectively, to yield substituted γ-butyrolactones.[56]

THE DICHLOROACETATE SYNTHESIS

Darzens has discovered a series of reactions starting with ethyl dichloroacetate which promises to be of wide applicability. The dichloro ester condenses with aldehydes and ketones in the presence of dilute magnesium amalgam to give excellent yields of α-chloro β-hydroxy esters which can be converted to glycidic esters or to α-chloroacrylic esters.[15,16,17]



[56] Chelintsey and Osetrova, *J. Gen. Chem. U.S.S.R.*, **7**, 2373 (1937) [*C.A.*, **32**, 2099 (1938)].

The α-chloro β-hydroxy esters are formed in almost theoretical yields from ketones. Aliphatic aldehydes, which with α-chloro esters give poor yields of glycidic esters, give yields of 40% to 68% of α-chloro β-hydroxy esters. Ethyl dibromoacetate may replace the dichloro ester, calcium and zinc amalgams the magnesium amalgam, and benzene may replace ether as solvent.[16]

The halohydrin esters are quantitatively converted into glycidic esters by treatment with one equivalent of sodium ethoxide. Alternatively, they may be dehydrated to α-chloroacrylates in high yield by phosphorus pentoxide.

The overall conversion of the halohydrin esters to disubstituted acetaldehydes may be effected by two paths as indicated by the above chart. The path involving hydrolysis of the chloroacrylate and decarboxylation of the resulting α-keto acid is recommended by Darzens.[17] The dichloro ester synthesis merits more study and wider use.

EXPERIMENTAL PROCEDURES

Methyl α-Methyl-α,β-epoxycyclohexylideneacetate. (Use of sodium methoxide.) [18] A solution of 49 g. (0.5 mole) of cyclohexanone and 98 g. (0.5 mole) of methyl α-chloropropionate in 200 ml. of anhydrous ether is placed in a flask which has been previously dried by heating with a flame while being swept out with dry nitrogen. The entire reaction is carried out in an atmosphere of dry nitrogen. The reactants are cooled to 5°, and 45.5 g. (0.8 mole) of commercial sodium methoxide (95% pure, The Matheson Company) is added over a period of one hour during which time the reaction mixture is cooled in an ice-water bath and vigorously stirred. The reaction mixture is permitted to warm slowly to room temperature and is stirred for twenty hours, after which the mixture is hydrolyzed by the addition of a cold solution of 30 ml. of concentrated hydrochloric acid in 200 ml. of water. The ether solution is separated and washed successively with two 100-ml. portions of water, 100 ml. of saturated sodium bicarbonate solution, 50 ml. of water, and 100 ml. of saturated sodium chloride solution. After filtration through anhydrous sodium sulfate and distillation of the ether, 78 g. (85%) of methyl α-methyl-α,β-epoxycyclohexylideneacetate is obtained by vacuum distillation, b.p. 116–118°/8.5 mm.

Ethyl α-Methyl-β-*p*-tolylglycidate. (Use of sodium ethoxide, bromo ester, and an aromatic aldehyde.) [57] To a solution of 90 g. (0.5 mole) of ethyl α-bromopropionate and 60 g. (0.5 mole) of *p*-tolualdehyde, cooled in an ice-salt bath, 34 g. (0.5 mole) of freshly prepared sodium ethoxide

[57] Ruzicka and Ehmann, *Helv. Chim. Acta*, **15**, 160 (1932).

is added over a period of three to four hours. The mixture is stirred overnight with cooling, two hours at room temperature, and finally warmed six hours in a water bath. Ice water is then added, the mixture is acidified with acetic acid, and the product is extracted with ether. After drying and removing the solvent 62.5 g. (56%) of the glycidic ester is obtained, b.p. 148–152°/12 mm.

Ethyl β-Methyl-β-phenylglycidate. (Use of sodium amide.) Detailed directions for the preparation of this ester in 62–64% yield from ethyl chloroacetate and acetophenone with sodium amide as the condensing agent are given in *Organic Syntheses*.[58]

Hydratropaldehyde. (Conversion of a glycidic ester to an aldehyde.) [58,59] To a stirred solution of 274 g. (6.85 moles) of sodium hydroxide in 770 ml. of water is added 708 g. (3.44 moles) of ethyl β-methyl-β-phenylglycidate. After being stirred for nine hours at 45–50°, the solution is acidified to Congo red with 6 *N* hydrochloric acid. The glycidic acid is extracted with benzene and distilled with superheated steam [59] at 180°. This treatment decarboxylates the glycidic acid over a period of four to five hours, the aldehyde being removed continuously as formed. The aldehyde is extracted from the distillate with benzene and is vacuum-distilled to yield 268 g. (58%) of product, b.p. 101–102°/21–22 mm. Alternatively [58] the original hydrolysate, acidified to Congo red, is steam-distilled at atmospheric pressure for about eighty hours, approximately 125 l. of distillate being collected. After extraction with benzene and distillation, the yield is 310 g. (67%).

Ethyl β-*p*-Chlorophenylglycidate. (Use of powdered sodium.) [46] Over a period of two hours a solution of 49 g. (0.45 mole) of ethyl chloroacetate and 60 g. (0.43 mole) of *p*-chlorobenzaldehyde is added to 10 g. (0.48 mole) of powdered sodium suspended in 150 ml. of xylene. Water is then added, and the xylene fraction containing the product is worked up as previously described. The pure product boils at 155–160°/4 mm.; yield 75 g. (66%).

Ethyl α-Chloro-β-hydroxy-β-phenylbutyrate. (Use of magnesium amalgam and ethyl dichloroacetate.) [16] A magnesium amalgam is prepared by warming a mixture of 7.5 g. of magnesium with 375 g. of mercury under a stream of hydrogen. The amalgam is cooled under hydrogen, and a solution of 36 g. (0.3 mole) of acetophenone and 48 g. (0.3 mole) of ethyl dichloroacetate in 300 ml. of anhydrous ether is added with stirring and cooling. After being stirred for six to ten hours the mixture is poured on ice containing acetic acid and the organic portion is worked up in the usual fashion. Vacuum distillation gives 68 g. (92%) of product, b.p. 166–167°/5 mm.

[58] Allen and Van Allen, *Org. Syntheses*, **24**, 82 (1944).
[59] Newman and Closson, *J. Am. Chem. Soc.*, **66**, 1553 (1944).

EXAMPLES OF THE DARZENS GLYCIDIC ESTER CONDENSATION

The literature has been covered through 1947. The compounds are listed according to the increasing carbon content of the empirical formula of the glycidic ester as in the *Chemical Abstracts Formula Index*.

The typical procedure involves slow addition of the condensing agent to a cooled mixture of the carbonyl compound and halo ester with or without a solvent. The condensing agents are:

A. The sodium alkoxide corresponding to the alkyl group of the halo ester.

B. Sodium amide.

C. Sodium, usually powdered.

TABLE I

Glycidic Esters

Carbonyl Component	Glycidic Ester Formula				Condensing Agent	Yield %	References *
	R′	R″	R‴	R⁗			
Formaldehyde	H	H	CH_3—	C_2H_5—	A	20–30	4
Acetaldehyde	CH_3—	H	H	C_2H_5—	C	—	19
Acetone	CH_3—	CH_3—	H	C_2H_5—	†	47 ‡	19
Acetone	CH_3—	CH_3—	H	C_2H_5—	C	53	19
					A	60	2
					B	59 §	14
Acetaldehyde	CH_3—	H	CH_3—	C_2H_5—	A	20–30	4
Propionaldehyde	C_2H_5—	H	H	C_2H_5—	A	20–30	4
Acetone	CH_3—	CH_3—	CH_3—	C_2H_5—	A	—	3
Butanone	C_2H_5—	CH_3—	H	C_2H_5—	A	56	44
					B	34	14, 60
Furfural	C_4H_3O—	H	H	C_2H_5—	C	—	61
					A	96(?)	20
Furfural	C_4H_3O—	H	CH_3—	CH_3—	A ‖	73	62
Mesityl oxide	C_4H_7—	CH_3—	H	C_2H_5—	A	58 ¶	63
Cyclopentanone	—$(CH_2)_4$—		H	C_2H_5—	A	41	64
Butanone	C_2H_5—	CH_3—	CH_3—	C_2H_5—	A	—	3
3-Methyl-2-butanone	*iso*-C_3H_7—	CH_3—	H	C_2H_5—	C	—	65
2-Pentanone	C_3H_7—	CH_3—	H	C_2H_5—	B	50	14
3-Pentanone	C_2H_5—	C_2H_5—	H	C_2H_5—	B	50	14
Benzaldehyde	C_6H_5—	H	H	CH_3—	A	54	18
Furfural	C_4H_3O—	H	CH_3—	C_2H_5—	A	50	4
Cyclohexanone	—$(CH_2)_5$—		H	C_2H_5—	A **	68	43
					A	65	4
Cyclohexanone	—$(CH_2)_5$—		CH_3—	CH_3—	A	85	18
Cyclopentanone	—$(CH_2)_4$—		CH_3—	C_2H_5—	A	35	43
3-Methylbutanal	*iso*-C_4H_9—	H	CH_3—	C_2H_5—	A	20–30	4
2-Pentanone	C_3H_7—	CH_3—	CH_3—	C_2H_5—	A	—	3
o-Chlorobenzaldehyde	*o*-C_6H_4Cl—	H	CH_3—	CH_3—	A	70	62
p-Chlorobenzaldehyde	*p*-C_6H_4Cl—	H	H	C_2H_5—	C	66	46
Benzaldehyde	C_6H_5—	H	H	C_2H_5—	A	50	4
					B	25	14
Acetophenone	C_6H_5—	CH_3—	H	CH_3—	A	70	21
					B	—	66
2-Methylcyclohexanone	—$CHCH_3(CH_2)_4$—		H	C_2H_5—	A	—	5
3-Methylcyclohexanone ††	—$CH_2CHCH_3(CH_2)_3$—		H	C_2H_5—	B ‡‡	—	47
3-Methylcyclohexanone	—$CH_2CHCH_3(CH_2)_3$—		H	C_2H_5—	A	—	5
4-Methylcyclohexanone	—$(CH_2)_2CHCH_3(CH_2)_2$—		H	C_2H_5—	A	—	5
4-Methylcyclohexanone	—$(CH_2)_2CHCH_3(CH_2)_2$—		CH_3—	CH_3—	A	60	67

* References 60–87 are on pp. 439–440.

† Ethyl chloroacetate was added to the sodium enolate of the ketone prepared from sodium amide in ether.

‡ The yield was based on the chloro ester.

§ An impure product containing chloro ester and chloro amide.

‖ The α-bromo ester was used.

¶ A mixture of methyl and ethyl esters was employed.

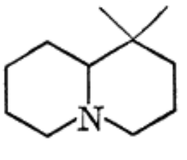
** This experiment was run at −80° with no solvent.

†† An optically active ketone was used, and an optically active aldehyde was obtained.

‡‡ The α-bromo ester was used.

TABLE I—*Continued*

GLYCIDIC ESTERS

Carbonyl Component	Glycidic Ester Formula				Condensing Agent	Yield %	References *
	R′	R″	R‴	R⁗			
Cyclohexanone	—$(CH_2)_5$—		CH_3—	C_2H_5—	A	—	6
3,4-Methylenedioxybenzaldehyde (piperonal)	$C_7H_5O_2$—	H	H	C_2H_5—	C	—	68
Benzaldehyde	C_6H_5—	H	CH_3—	C_2H_5—	A	50, 71	4, 18
p-Tolualdehyde	C_7H_7—	H	H	C_2H_5—	C	—	46
Acetophenone	C_6H_5—	CH_3—	H	C_2H_5—	A	60–64	2, 58
					B	—, 64	14, 69
o-Methoxybenzaldehyde	*o*-C_7H_7O—	H	CH_3—	CH_3—	A	75	62
m-Methoxybenzaldehyde	*m*-C_7H_7O—	H	CH_3—	CH_3—	A	82	62
p-Methoxybenzaldehyde	*p*-C_7H_7O—	H	H	C_2H_5—	C	—	46, 68
1-Cyclohexenyl methyl ketone	C_6H_5—	CH_3—	H	C_2H_5—	A	—	9
6-Methyl-5-hepten-2-one	C_6H_{11}—	CH_3—	H	C_2H_5—	A §§	45	70, 71
					A ‖‖	30	70
6-Methyl-6-hepten-2-one	C_6H_{11}—	CH_3—	H	C_2H_5—	A	—	72
2-Methylcyclohexanone	—$CHCH_3(CH_2)_4$—		CH_3—	C_2H_5—	A	—	6
3-Methylcyclohexanone	—$CH_2CHCH_3(CH_2)_3$—		CH_3—	C_2H_5—	A	—	6
3-Methylcyclohexanone (active)					B	—	47
4-Methylcyclohexanone	—$(CH_2)_2CHCH_3(CH_2)_2$—		CH_3—	C_2H_5—	A	—	6
2-Octanone	C_6H_{13}—	CH_3—	H	C_2H_5—	C	41	49*a*
6-Methyl-2-heptanone	C_6H_{13}—	CH_3—	H	C_2H_5—	A	—	2
3,4-Methylenedioxybenzaldehyde (piperonal)	$C_7H_5O_2$—	H	CH_3—	C_2H_5—	A ¶¶	48	73
					A	—	4
Acetophenone	C_6H_5—	CH_3—	CH_3—	C_2H_5—	A	—, 35	3, 18
					B	—	14
Phenylacetone	C_7H_7—	CH_3—	H	C_2H_5—	A	60–63	2
					A	—	74
p-Tolualdehyde	C_7H_7—	H	CH_3—	C_2H_5—	A	56	57
p-Ethylbenzaldehyde	C_8H_9—	H	H	C_2H_5—	C	—	46
2,4-Dimethylbenzaldehyde	C_8H_9—	H	H	C_2H_5—	C	—	46
Propiophenone	C_6H_5—	C_2H_5—	H	C_2H_5—	A	42	45
					B	—	14
p-Tolyl methyl ketone	C_7H_7—	CH_3—	H	C_2H_5—	A	—, 66	75, 76
p-Methoxybenzaldehyde	$CH_3OC_6H_4$—	H	CH_3—	C_2H_5—	A	—	4
p-Methoxybenzaldehyde	$CH_3OC_6H_4$—	H	C_2H_5—	CH_3—	A	72	62
p-Methoxyacetophenone	$CH_3OC_6H_4$—	CH_3—	H	C_2H_5—	C	—	69
2,3-Dimethoxybenzaldehyde	$(CH_3O)_2C_6H_3$—	H	H	C_2H_5—	A	—	77
"1-Ketoöctahydropyridocoline"			H	C_2H_5—	B	40 ***	78

* References 60–87 are on pp. 439–440.

§§ Petroleum ether, b.p. 100–120°, was used as solvent.

‖‖ No solvent was employed.

¶¶ The α-bromo ester was used.

*** Neither the glycidic acid nor the aldehyde could be prepared from this ester.

TABLE I—*Continued*

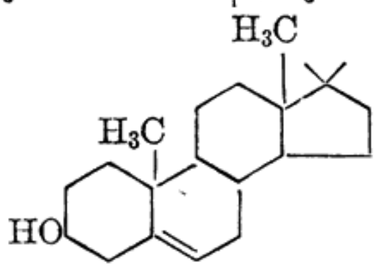
GLYCIDIC ESTERS

Carbonyl Component	Glycidic Ester Formula R′	R″	R‴	R⁗	Condensing Agent	Yield %	References *
3-Methylcyclohexanone	—$CH_2CHCH_3(CH_2)_3$—		C_2H_5—	C_2H_5—	B	—	47
2-Dimethylaminomethyl cyclohexanone	—$CHCH_2N(CH_3)_2(CH_2)_4$—		H	C_2H_5—	A	43–58	21
Acetone	CH_3—	CH_3—	H	$CH_3(CH_2)_3CH(C_2H_5)CH_2$—	A	46	67
2-Nonanone	C_7H_{15}—	CH_3—	H	C_2H_5—	A	60–63	2
2-Octanone	C_6H_{13}—	CH_3—	CH_3—	C_2H_5—	A	—	3
3,4-Dimethoxybenzaldehyde	$(CH_3)_2C_6H_3$—	H	CH_3—	CH_3—	A	70	62
Benzaldehyde	C_6H_5—	H	C_2H_5—	C_3H_7—	A	67	67
p-Isopropylbenzaldehyde	C_9H_{11}—	H	H	C_2H_5—	C, A	—	20, 46
2,4,6-Trimethylbenzaldehyde	C_9H_{11}—	H	H	C_2H_5—	A	—	20
2,4,5-Trimethylbenzaldehyde	C_9H_{11}—	H	H	C_2H_5—	A	—	20
p-Methylacetophenone	C_7H_7—	CH_3—	CH_3—	C_2H_5—	A	—	3
Propiophenone	C_6H_5—	C_2H_5—	H	*iso*-C_3H_7—	A	58	67
Isobutyrophenone	C_6H_5—	*iso*-C_3H_7—	H	C_2H_5—	B	—	23
p-Methylacetophenone	C_7H_7—	CH_3—	H	*iso*-C_3H_7—	A	47	67
Butyrophenone	C_6H_5—	C_3H_7—	H	C_2H_5—	A	60–63	2
p-Ethylacetophenone	C_8H_9—	CH_3—	H	C_2H_5—	A	60–63	2
4-Phenyl-2-butanone	C_8H_9—	CH_3—	H	C_2H_5—	C	—	69
p-Methoxybenzaldehyde	$CH_3OC_6H_4$—	H	*iso*-C_3H_7—	CH_3—	A †††	70	62
β-Decalone	β-$C_{10}H_{16}$<		H	C_2H_5—	A	90, 71	12, 49*a*
					C	80	69
2-Nonanone	C_7H_{15}—	CH_3—	CH_3—	C_2H_5—	A	—	3
2-Decanone	C_8H_{17}—	CH_3—	H	C_2H_5—	C	—	69
5,6,7,8-Tetrahydro-1-naphthaldehyde	$C_{10}H_{11}$—	H	H	C_2H_5—	C	—	46
p-*sec*-Butylbenzaldehyde	$C_{10}H_{13}$—	H	H	C_2H_5—	C	—	46
2-Methyl-5-isopropylbenzaldehyde	$C_{10}H_{13}$—	H	H	C_2H_5—	A	—	20
p-Isopropylbenzaldehyde	C_9H_{11}—	H	CH_3—	C_2H_5—	A	40	79
p-Isopropylacetophenone	C_9H_{11}—	CH_3—	H	C_2H_5—	C	—	69
β-Decalone	β-$C_{10}H_{16}$<		CH_3—	C_2H_5—	A	—	12
2-Undecanone	C_9H_{19}	CH_3—	H	C_2H_5—	A	60–63	2, 75
					C	—	69
Benzophenone	C_6H_5—	C_6H_5—	H	CH_3—	A	—	41
Methyl 1-naphthyl ketone	1-$C_{10}H_7$—	CH_3—	H	C_2H_5—	A	45	7
Methyl 2-naphthyl ketone	2-$C_{10}H_7$—	CH_3—	H	C_2H_5—	A	—	7
Isobutylacetophenone ‡‡‡	$C_{10}H_{13}$—	CH_3—	H	C_2H_5—	A	60–63	2
2,2-Dimethyl-3-(carbethoxymethyl)-cyclobutyl methyl ketone	$C_{10}H_{17}O_2$—	CH_3—	H	C_2H_5—	A	50 §§§	80
2-Isopropyl-2-(carbethoxymethyl)-cyclopropyl methyl ketone	$C_{10}H_{17}O_2$—	CH_3—	H	C_2H_5—	A	32 ‖‖‖	81

* References 60–87 are on pp. 439–440.
††† The bromo ester was used.
‡‡‡ The position of the isobutyl group was not stated.
§§§ Forty-six per cent of the keto ester was recovered.
‖‖‖ Twenty-five per cent of the keto ester was recovered.

TABLE I—*Continued*

GLYCIDIC ESTERS

Carbonyl Component	Glycidic Ester Formula				Condensing Agent	Yield %	References *
	R′	R″	R‴	R⁗			
2-Undecanone	C_9H_{19}—	CH_3—	CH_3—	C_2H_5—	A	—	3
Benzophenone	C_6H_5—	C_6H_5—	H	C_2H_5—	A	75 ¶¶¶	19, 40, 41, 42
2,4-Diisopropylbenzaldehyde	$C_{12}H_{17}$	H	H	C_2H_5—	C	—	46
4-(*p*-Isopropylphenyl)-2-butanone	$C_{11}H_{15}$—	CH_3—	H	C_2H_5—	C	—	69
α-Ionone	$C_{11}H_{17}$—	CH_3—	H	C_2H_5—	A	34	47*a*, 63*a*
β-Ionone	$C_{11}H_{17}$—	CH_3—	H	C_2H_5—	A	55, 80	47*a*,*b*, 63*b*, 82
Tetrahydroionone	$C_{11}H_{21}$—	CH_3—	H	C_2H_5—	C	73	69
Acetone	CH_3—	CH_3—	*n*-$C_{10}H_{21}$—	C_2H_5—	A	70	13
6,10-Dimethyl-2-undecanone	$C_{11}H_{23}$—	CH_3—	H	C_2H_5—	C	69	69
p-Methylbenzophenone	C_7H_7—	C_6H_5—	H	C_2H_5—	B	—	42
p-Methyoxybenzophenone	C_7H_7O—	C_6H_5—	H	C_2H_5—	B	—	42
5-(2,2,6-Trimethylcyclohexenyl)-3-pentanone	$C_{11}H_{21}$—	C_2H_5—	H	C_2H_5—	C	—	69
Dibenzyl ketone	C_7H_7—	C_7H_7—	H	C_2H_5—	A	—	83
3-Methoxy-4-benzyloxybenzaldehyde	$C_{14}H_{13}O_2$	H	CH_3—	C_2H_5—	****	—	84
Cyclohexanone	—$(CH_2)_5$—		*n*-$C_{10}H_{21}$—	C_2H_5—	A	—	13
Acetophenone	C_6H_5—	CH_3—	*n*-$C_{10}H_{21}$—	C_2H_5—	A	—	13
Dehydroandrosterone			CH_3—	C_2H_5—	A	—	25, 85

* References 60–87 are on pp. 439–440.

¶¶¶ The product is an *α*-keto ester, not a glycidic ester.

**** The condensing agent was not mentioned. A bromo ester was used.

TABLE II

Glycidic Amides

The procedures are similar to those used in the glycidic ester reactions. The condensing agents used are the following: A. Sodium ethoxide. B. Sodium amide. C. Sodium.

Carbonyl Compound	Glycidic Amide Formula				Condensing Agent	Yield %	References *
	R′	R″	R‴	R⁗			
Acetone	CH_3—	CH_3—	H	NH_2—	C	80	24
					A	55	86
3-Pentanone	C_2H_5—	C_2H_5—	H	NH_2—	A †	—	86
					B †	—	86
Cyclohexanone	—$(CH_2)_5$—		H	NH_2—	—	—	86
Benzaldehyde	C_6H_5—	H	H	NH_2—	—	—	86
Acetone	CH_3—	CH_3—	H	$N(C_2H_5)_2$—	B	80	24
Benzaldehyde	C_6H_5—	H	CH_3—	$NHCH_3$—	A ‡	75–80	24
Propiophenone	C_6H_5—	C_2H_5—	H	NH_2—	A	80	24
1-Phenyl-2-propanone	C_7H_7—	CH_3—	H	NH_2—	—	—	86
1-Phenoxy-2-propanone	C_7H_7O—	CH_3—	H	NH_2—	—	—	86
Acetophenone	C_6H_5—	CH_3—	H	$N(CH_3)_2$—	—	—	86
Citral	C_9H_{15}—	H	H	NH_2—	A	70	24
Benzaldehyde	C_6H_5—	H	H	NHC_6H_5—	A	—	28c

* References 60–87 are on pp. 439–440.

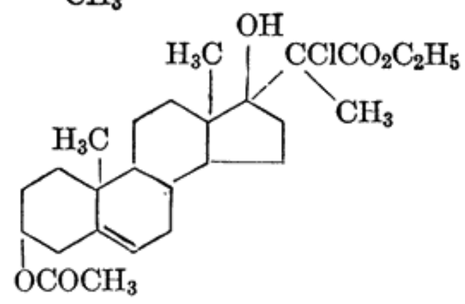
† Procedure A gave an amide m.p. 104°; procedure B, an amide m.p. 148°.

‡ The α-bromoamide was used.

TABLE III

α-Chloro β-Hydroxy Esters

The procedure involves the addition of a mixture of ketone and α,α-dichloro ester in ether to dilute (1 to 50) magnesium amalgam. All the α-chloro β-hydroxy esters were converted in high yield to epoxy esters by treatment with alkaline reagents.

Carbonyl Component	Product	Yield %	References *
Acetaldehyde	$CH_3CHOHCHClCO_2C_2H_5$	40	17
Acetone	$(CH_3)_2COHCHClCO_2C_2H_5$	—	15, 16
Isobutyraldehyde	$(CH_3)_2CHCHOHCHClCO_2C_2H_5$	68	17
Cyclopentanone	$(CH_2)_4{=}COHCHClCO_2C_2H_5$	—	17
Cyclohexanone	$(CH_2)_5{=}COHCHClCO_2C_2H_5$	97	17
Benzaldehyde	$C_6H_5CHOHCHClCO_2C_2H_5$	—	17
Heptaldehyde	$CH_3(CH_2)_5CHOHCHClCO_2C_2H_5$	57	17
Acetophenone	$C_6H_5COHCHClCO_2C_2H_5$ $\vert$ CH_3	95	16
Dehydroandrosterone acetate †		—	87

* References 60–87 are on pp. 439–440.

† This reaction failed when dehydroandrosterone was used, Ercoli and Mamoli, *Chimica e Industria*, **1937,** 435.

REFERENCES TO TABLES

[60] Neustadter, *Monatsh.*, **27,** 889 (1906).

[61] Asahina and Fujita, *J. Pharm. Soc. Japan*, No. 490, 1084 (1922) [*C.A.*, **17,** 2578 (1923)].

[62] Wolf, Ger. pat. 702,007 [*C.A.*, **36,** 95 (1942)].

[63] (*a*) Ishikawa and Matsuura, *Sci. Repts. Tokyo Bunrika Daigaku*, **3A,** 173 (1937) [*C.A.*, **31,** 7851 (1937)]; (*b*) Cymerman, Heilbron, Jones, and Lacey, *J. Chem. Soc.*, **1946,** 500.

[64] Newman, *J. Am. Chem. Soc.*, **57,** 732 (1935).

[65] Brunner and Farmer, *J. Chem. Soc.*, **1937,** 1039.

[66] von Auwers, *Ann.*, **415,** 147 (1918).

[67] Newman, Magerlein, and Wheatley, *J. Am. Chem. Soc.*, **68,** 2112 (1946).

[68] Rosenmund and Dornsaft, *Ber.*, **52,** 1740 (1919).

[69] Knorr and Weissenborn, Ger. pat. 602,816 [*C.A.*, **29,** 1438 (1935)].

[70] Doeuvre, *Bull. soc. chim. France*, [4] **45,** 710 (1929).

[71] Fester and Pucci, *Ber.*, **69,** 2017 (1936).

[72] Verley, *Bull. soc. chim. France*, [4] **35,** 608 (1924).

[73] Elks and Hey, *J. Chem. Soc.*, **1943,** 15.

[74] Darzens, U. S. pat. 830,213 [*C.A.*, **1**, 251 (1907)].
[75] Darzens, Ger. pat. 174,279 [*C.A.*, **1**, 950 (1907)].
[76] Dutta, *J. Indian Chem. Soc.*, **18**, 233 (1941).
[77] Mauthner, *J. prakt. Chem.*, [2] **148**, 95 (1937).
[78] Clemo, Romage, and Raper, *J. Chem. Soc.*, **1931**, 3190.
[79] Bradfield, Pritchard, and Simonsen, *J. Chem. Soc.*, **1937**, 760.
[80] Ruzicka and Trebler, *Helv. Chim. Acta*, **4**, 666 (1921).
[81] Ruzicka and Koolhaas, *Helv. Chim. Acta*, **15**, 944 (1932).
[82] Milas, U. S. pat. 2,369,156 [*C.A.*, **39**, 5043 (1945)]; U. S. pats. 2,369,160–2,369,167 incl. [*C.A.*, **39**, 5046 (1945)]; U. S. pat. 2,415,834 [*C.A.*, **41**, 3483 (1937)].
[83] Scheibler and Tutundzitsch, *Ber.*, **64**, 2916 (1931).
[84] Robinson and Lowe, Eng. pat. 519,894 [*C.A.*, **36**, 875 (1942)].
[85] Yarnall and Wallis, *J. Am. Chem. Soc.*, **59**, 951 (1937); Yarnall and Wallis, *J. Org. Chem.*, **4**, 270 (1939).
[86] Fourneau, Billeter, and Bovet, *J. pharm. chim.*, **19** (1934) [*C.A.*, **28**, 5179 (1934)].
[87] Miescher and Kagi, *Helv. Chim. Acta*, **22**, 184 (1939); *Chemistry & Industry*, **57**, 276 (1938).