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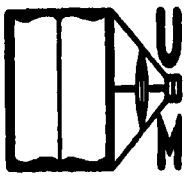
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AUTHOR JOHN ANDREW FAUST

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ANTISPASMODICS. XI

by

John Andrew Faust

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Committee in charge:

Professor F. F. Blicke, Chairman
Professor W. E. Bachmann
Professor F. E. Bartell
Professor H. B. Lewis
Professor E. F. Barker

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John Andrew Faust

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GENERAL INTRODUCTION

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Basic-alkyl esters of diaryl- and diarylhydroxyacetic acids are of considerable pharmacological interest, and one of these esters, β-diethylaminoethyl diphenylacetate hydrochloride, is the well-known antispasmodic Trasentin. In addition to their antispasmodic activity, a number of the esters are strong local anesthetics[1] and mydriatics[2,3,4].

In many instances it has been found that the basic esters of diphenylhydroxyacetic acid are far more potent as antispasmodics than the corresponding esters of diphenylacetic acid. It is highly probable that esters of the former acid would find clinical use if it were not for an undesirable side effect - stimulation of the central nervous system. It has not been found possible to retain the high potency of the esters of the hydroxy acids, and to free them from this side effect, by the substitution of an acetoxy or alkoxy radical for the hydroxy group[5].

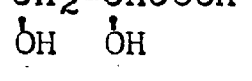
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(1) Goodman, Gilman, Thomas, Hahn and Prutting, J. Pharmacol. Exptl. Therap., 74, 290 (1942).
(2) Blicke and Kaplan, J. Am. Chem. Soc., 65, 1967 (1943).
(3) Blicke and Maxwell, J. Am. Chem. Soc., 64, 431 (1942).
(4) Ford-Moore and Ing, J. Chem. Soc., 55 (1947).
(5) Blicke and Maxwell, J. Am. Chem. Soc., 64, 428 (1942).

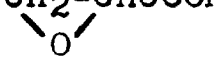
Since basic esters of diphenylhydroxyacetic acid are so active, it seemed especially desirable to investigate analogous derivatives, and these latter substances are the subject of this dissertation.

The chemistry and pharmacology of certain basic esters of phenylhydroxypropionic acids have already been reported in the literature. Basic esters of α-phenyl-α-hydroxypropionic (atrolactic acid), α-phenyl-β-hydroxypropionic (tropic acid), β-phenyl-α-phenylpropionic, β-phenyl-β-hydroxypropionic and β,β-diphenyl-β-hydroxypropionic acids have been prepared and examined for local anesthetic and mydriatic properties[2].

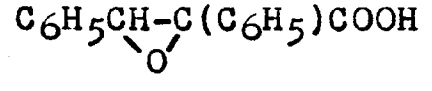
In the study of basic esters of substituted propionic acids, it is possible to include not only esters which are analogous to the highly active esters of diphenylhydroxyacetic acid, that is, esters of diphenylhydroxypropionic acids, but also esters of oxygenated diphenylpropionic acids in which the oxygen atom is not present in the form of a hydroxyl group. Such esters are those of diphenylepoxypropionic acids, more commonly known as diphenylglycidic acids. The parent acid, epoxypropionic acid or glycidic acid, may be regarded as an anhydride of α,β-dihydroxypropionic acid (glyceric acid).



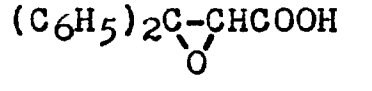
α,β-Dihydroxypropionic acid, glyceric acid.



Epoxypropionic acid, glycidic acid.



α,β-Diphenylglycidic acid.



β,β-Diphenylglycidic acid.

As far as we are aware, no basic ester of an epoxy acid has ever been described, although amides of epoxy acids have been prepared for testing as hypnotic agents by Fourneau and Billeter[6].

Since the preparation and properties of diphenylglycidic acids are similar to those of the older and more thoroughly investigated glycidic and phenylglycidic acids, the chemistry of these latter compounds is reviewed on the following pages.

Although glycidic and phenylglycidic acids have relatively simple formulas, controversies relative to their structures extended over a period of years.

Glycidic Acid.

In 1879, Werigo and Melikoff[7] reported that glyceric acid, $CH_2(OH)CH(OH)COOH$, was converted, by the action of either phosphorous pentachloride or hydrochloric acid, to a liquid monochlorolactic acid. The position of the chlorine atom was not known at that time. Later, Melikoff[8] showed that this same acid was obtained when hypochlorous acid reacted with acrylic acid, $CH_2=CHCOOH$. In studying the properties and reactions of this monochlorolactic acid, Melikoff[9]

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(6) Fourneau and Billeter, Bull. soc. chim., (5) 6, 1616 (1939).
(7) Werigo and Melikoff, Ber., 12, 178 (1879).
(8) Melikoff, Ber., 12, 2227 (1879).
(9) Melikoff, Ber., 13, 271 (1880).

discovered that alcoholic potassium hydroxide, followed by acidification with sulfuric acid, converted it into a new acid, which he called oxyacrylic acid but which later became known as glycidic acid*.

CH_2=CHCOOH $\xrightarrow{HOCl}$ chlorolactic acid $\xrightarrow[2)\ H_2SO_4]{1)\ KOH}$ oxyacrylic acid (glycidic acid)

Melikoff described the properties of his new acid in some detail. He stated that it was a strongly acidic oil having the same empirical formula as pyruvic acid, $CH_3COCOOH$, but unlike the latter acid, it did not become red when treated with ferrous sulfate. It was easily converted, by water, into glyceric acid and, by hydrochloric acid, into a solid chlorolactic acid whose properties were different from those of the liquid chlorolactic acid from which the glycidic acid had been prepared.

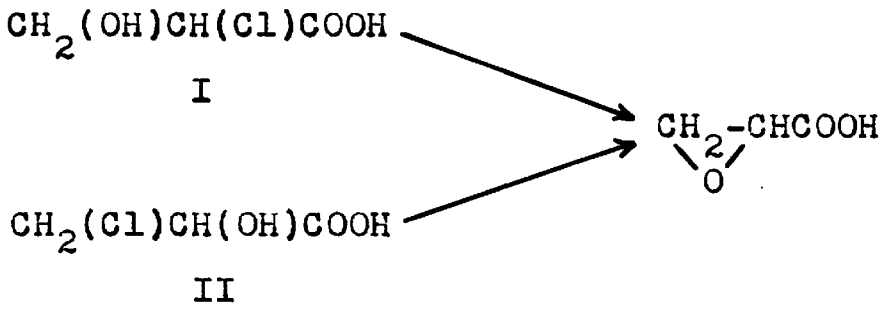
Glycidic acid was next prepared by Erlenmeyer(10) who made it by treating the chlorolactic acid, obtained from the

---

* Melikoff and Erlenmeyer published arguments concerning a proper name for this acid. Erlenmeyer (Ber., 13, 457 (1880)) believed that oxypropionic acid was a better name than oxyacrylic acid, which was used by Melikoff. Subsequent studies by Melikoff (Ber., 13, 956 (1880)) led him to look upon the acid as being an inner anhydride of glyceric acid, and he suggested, therefore, since the inner anhydride of glycerin was known as glycide, the epoxy acid should logically be called glycidic acid. Erlenmeyer (Ber., 13, 1077 (1880)) admitted that the name oxypropionic acid could be confused with both α- and β-ketopropionic acids, $HCOCH_2COOH$ and $CH_3COCOOH$, and agreed that the name glycidic acid should be applied to the epoxy acid. In the same article, he suggested that Glaser's phenyloxyacrylic acid, which is discussed later, should be referred to as phenylglycidic acid.

(10) Erlenmeyer, Ber., 13, 457 (1880).

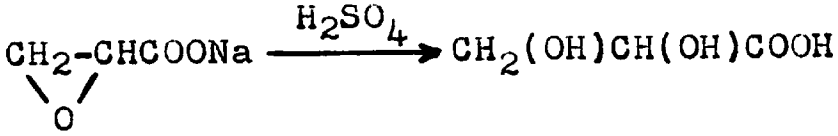
oxidation of monochlorohydrin, $CH_2(OH)CH(OH)CH_2Cl$, with alcoholic potassium hydroxide. Because of the method of preparation, Erlenmeyer stated that his acid was β-chlorolactic acid, and that, since it differed distinctly from the chlorolactic acid of Melikoff, Melikoff's acid must have been the α-chloro isomer. Erlenmeyer pointed out that it was logical to expect the same epoxy acid from both isomers, and he was the first to assign to it the correct structural formula.

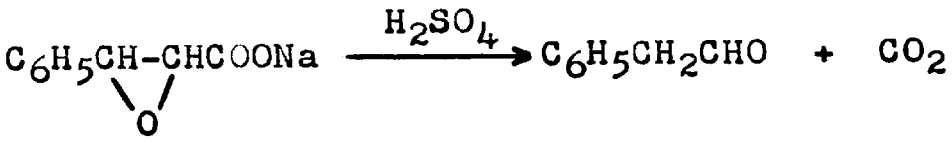


In the same paper, he reported that the sodium salt of this acid was converted mainly into glyceric acid when treated with warm, dilute sulfuric acid, and that only a trace of acetaldehyde was formed in this reaction. He claimed that in this respect glycidic acid differed from phenylglycidic acid*, since the latter, in the form of its sodium salt, was converted into phenylacetaldehyde by the same treatment.

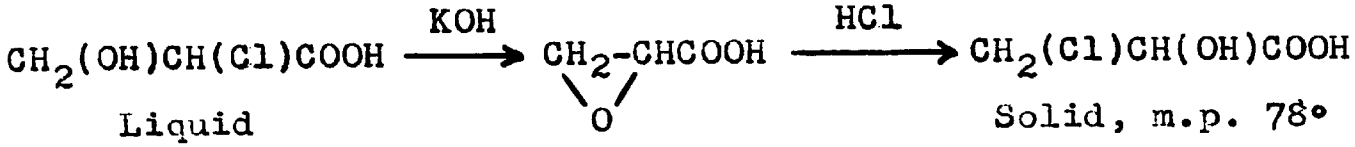
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* According to Lipp (Ber., 16, 1286 (1883)), and to Plöchl and Mayer (Ber., 30, 1600 (1907)), both phenylglyceric acid and phenylacetaldehyde are formed when phenylglycidic acid is heated in the presence of aqueous sulfuric acid.

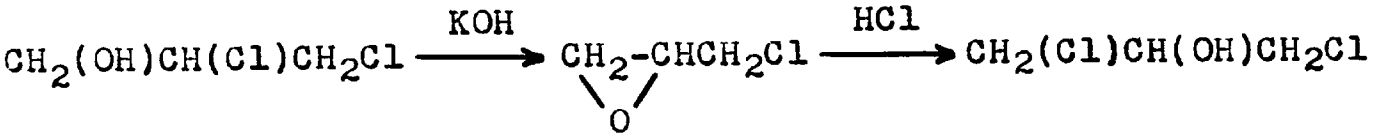




Melikoff[11] at first* believed his initial chlorolactic acid (I) was the α-chloro isomer, and showed that it could be converted into the β-isomer by the following series of reactions in which glycidic acid was the probable intermediate.



This series of reactions was stated to be analogous to the following reactions, which were well-known at that time.



Hydrogen bromide adds to glycidic acid in the same manner as hydrogen chloride, and the product is β-bromolactic acid[12].

---

(11) Melikoff, Ber., 13, 956 (1880).

* Soon thereafter (Ber., 13, 2153 (1880)), he found both isomeric chlorolactic acids in his oily chlorolactic acid (I), and they were separated by fractional crystallization of their zinc salts from alcohol. The properties of the isomers obtained from this separation agreed with those previously reported for them; the α-chloro-isomer was an oil, whereas the β-compound was a solid, m.p. 78°.

(12) Melikoff, Ber., 13, 958 (1880); Freudenburg, Ber., 47, 2027 (1914).

It was found early that glycidic acid reacts with ammonia, and this reaction deserves brief mention, since it was used as a tool in attempts to establish the structures of the chlorolactic acids. Melikoff[11] reacted his α-chlorolactic acid with ammonia, and obtained an amino acid whose water solubility was different from that of serine, $CH_2(OH)CH(NH_2)COOH$, the expected product. To explain this unexpected result, he suggested that ammonia, because of its basicity, might first convert the chloro acid into glycidic acid, which would then add ammonia to form β-aminolactic acid, the isomer of serine.

$$CH_2(OH)CH(Cl)COOH \xrightarrow{NH_3} CH_2\text{-}CHCOOH \xrightarrow{NH_3} CH_2(NH_2)CH(OH)COOH$$

In order to support this claim, Melikoff treated glycidic acid with ammonia, and obtained an amino compound, which he did not identify, but stated that he intended to study it further.

Meanwhile, Erlenmeyer[13] also studied the reaction between glycidic acid and ammonia, and found that the amino compound formed was identical with the amino acid which he had prepared by the reaction between ammonia and β-chlorolactic acid and which Melikoff had obtained from the α-chlorolactic acid in the same manner. Thus, Erlenmeyer showed that Melikoff's claim concerning the intermediate formation of a glycidic acid in these reactions was correct. Melikoff[14] confirmed these experiments. He felt that, since halogen

(13) Erlenmeyer, Ber., 13, 1077 (1880).
(14) Melikoff, Ber., 13, 1265 (1880).

acids reacted with glycidic acid to form β-halolactic acids, ammonia had reacted to produce a β-aminolactic acid and, since this acid differed from serine, serine must be an α-aminoacid.

Melikoff[15] extended his general studies of glycidic acids by the preparation of its higher homologues, α- and β-methyl-glycidic acids, $CH_3CH\text{-}CHCOOH$ and $CH_2\text{-}C(CH_3)COOH$, as well as α,β-dimethylglycidic acid, $CH_3CH\text{-}C(CH_3)COOH$.

In general, he found that these epoxy acids show the same reactions as the parent glycidic acid.

The ethyl esters of glycidic acid and its above-mentioned homologues were prepared and studied by Melikoff and Zelinsky[16]. These esters were obtained by the interaction of a salt of the acid, usually either the potassium or silver salt, and ethyl iodide. The esters were described as colorless oils which boiled at atmospheric pressure without decomposition.

Glycidic acid possesses an asymmetric carbon atom and therefore should exist in dextro- and levo-rotatory forms. These optical isomers, in the form of their potassium salts, have been prepared from dextro- and levo-bromolactic acids

---

(15) Melikoff, Ann., 234, 197 (1886).
(16) Melikoff and Zelinsky, Ber., 21, 2052 (1888).

by Abderhalden and Eichwald[17] by means of cold alcoholic potassium hydroxide.

Phenylglycidic Acid.

Two isomeric phenylglycidic acids should be capable of existence: the α- and β-phenylglycidic acids. Only the β-phenyl derivative has been described in the literature, and is the one discussed in this dissertation*.

Interest in phenylglycidic acid developed through the study of cinnamic acid, $C_6H_5CH=CHCOOH$, a substance which had been obtained from plant products as early as 1839. Balsams, resins and the leaves and roots of certain plants are natural sources of cinnamic acid. Balsams have been used from the earliest times for the preparation of perfumes and as medicaments because of their healing and soothing effects. It is very probable that some of the valuable properties of balsams are due, at least to some extent, to the presence of cinnamic acid.

During the course of the early studies of the chemistry of cinnamic acid and its derivatives, Glaser[18] treated both phenylchloro- and phenylbromolactic acids** with alcoholic

---

(17) Abderhalden and Eichwald, Ber., 48, 113 (1915).

* It seems that ethyl α-phenylglycidate would be obtained by interaction of formaldehyde and ethyl α-chlorophenylacetate. The only instance in the literature in which formaldehyde has been used in this type of reaction is that in which formaldehyde was allowed to react with ethyl α-chloropropionate with the formation of ethyl α-methylglycidate (Darzens, Compt. rend., 142, 214 (1906)).

(18) Glaser, Ann., 147, 78 (1868).

** The exact structures of these compounds were not known with certainty at that time.

potassium hydroxide and obtained, in the form of its potassium salt, a new acid which he called phenyloxyacrylic acid. He found that, although various salts of this acid were stable and could be analyzed, the free acid was extremely unstable at ordinary temperature. Only by working at a low temperature was he able to obtain the free acid in solid form; however, it soon decomposed into carbon dioxide and a resinous material. Steam distillation converted it into carbon dioxide and a volatile oil, C_8H_8O, which he suggested was oxystyrene*. The fact that the free acid did not react with cold hydrogen chloride, as did lactic acid, led him to believe that the third oxygen atom of the acid was not present in the form of a hydroxyl group but that it "satisfied both affinities of the cinnamic acid molecule". He ventured no further than to propose the partial structural formula, $C_6H_5-C_2H_2O-COOH$, for phenyloxyacrylic acid.

Glaser also prepared the ethyl ester of his acid by the reaction of its silver salt with ethyl iodide; he reported that the ester boiled at 273° with some decomposition.

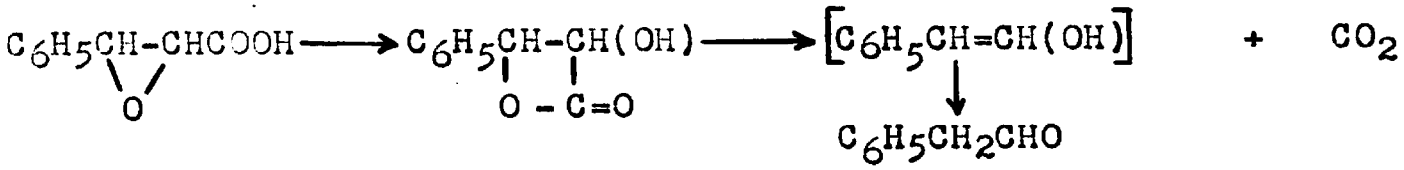
Later, Erlenmeyer, Sr.[19] expressed the opinion that Glaser's phenyloxyacrylic acid was phenylglycidic acid, $C_6H_5CH(O)CHCOOH$, and based his opinion on the manner in which

---

* Oxystyrene or styrene oxide, $C_6H_5CH(O)CH_2$, was not actually known until 1905 when it was described by Fourneau and Tiffeneau (Compt. rend., 140, 1595 (1905)).

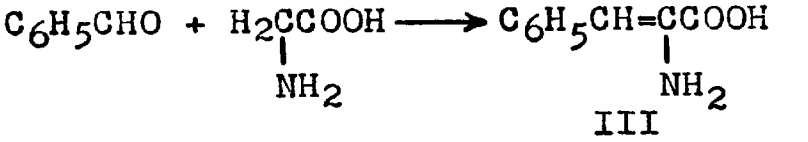
(19) Erlenmeyer, Sr., Ber., 13, 305 (1880).

Glaser had synthesized the acid, and on its behavior. Furthermore, he suggested that its decomposition product, called oxystyrene by Glaser, was phenylacetaldehyde, the formation of which he explained by the following series of reactions.



This author believed that all 1,2-unsaturated secondary and tertiary alcohols are unstable, and rearrange to aldehydes and ketones respectively. He cited other examples[20] as added evidence for this belief.

In 1883, Plöchl[21] described his experiments, which began with attempts to synthesize α-aminocinnamic acid. α-Chlorocinnamic acid was known at that time, but it could not be condensed with ammonia to form the amino acid. Plöchl hoped to be able to obtain α-aminocinnamic acid (III) by interaction of benzaldehyde with glycine, but only gums were formed by this process.

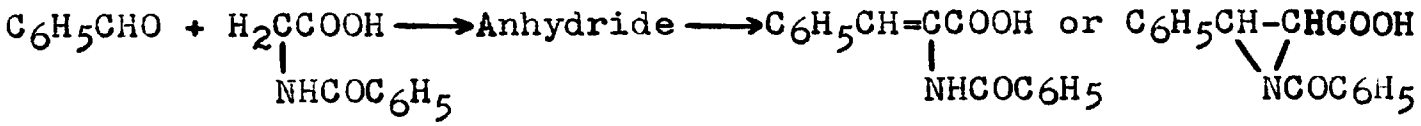


He had better success when he substituted hippuric acid (benzoylglycine) for glycine. However, the reaction product was not α-benzoylcinnamic acid (IV), but an anhydride, which

---

(20) Erlenmeyer, Sr., Ber., 14, 320 (1881).
(21) Plöchl, Ber., 16, 2815 (1883).

he assumed had been formed by the loss of one molecule of water from two molecules of (IV); upon hydrolysis, (IV) was formed from the anhydride. Plöchl preferred formula (IV') rather than (IV) for the acid, which he obtained by hydrolysis of the anhydride, since the acid would neither add hydrogen bromide nor form a nitroso derivative with nitrous acid.



IV IV'

He called this acid benzoylimidocinnamic acid and, in a later publication[22], described some of its derivatives and reactions*, by which he claimed to have prepared α-aminocinnamic acid**.

After a series of studies, Erlenmeyer, Jr.[23] discovered the true nature of Plöchl's anhydride and its hydrolytic

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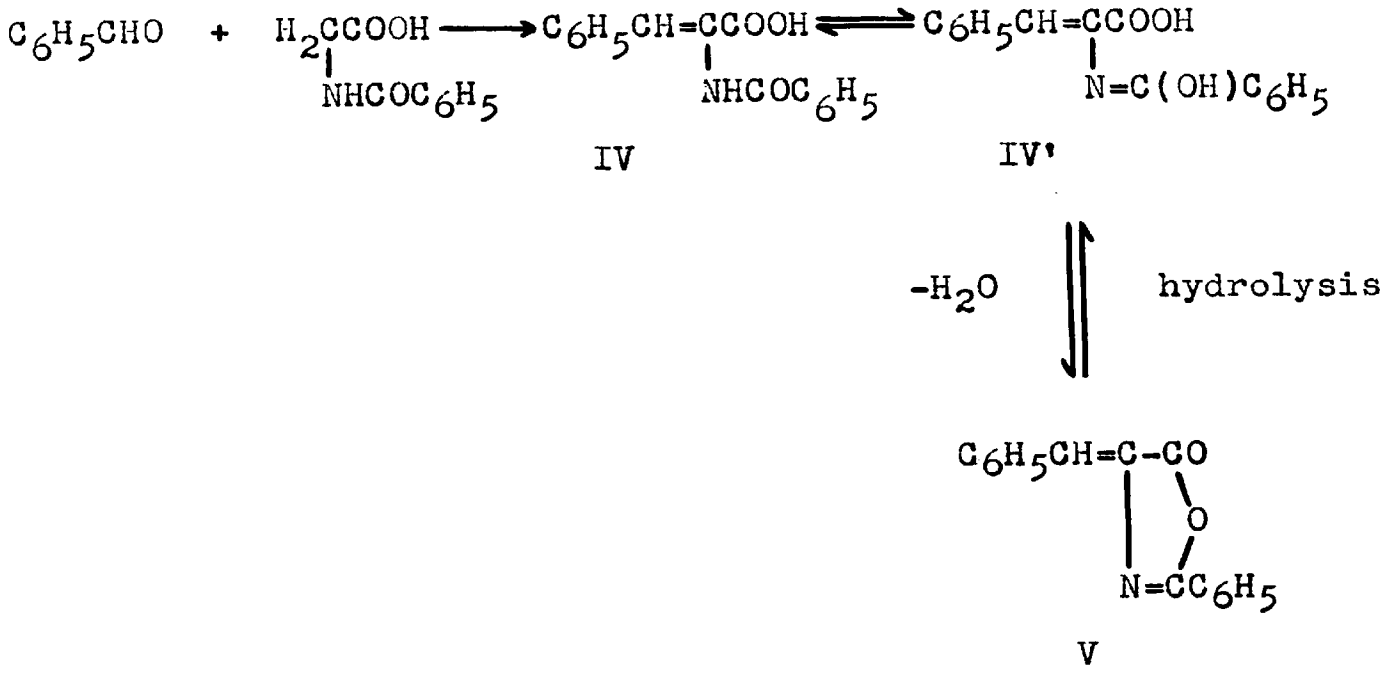
(22) Plöchl, Ber., 17, 1616 (1884).

* These reactions were also discussed by Erlenmeyer and Kunlin (Ann., 307, 146 (1899); see also Ber., 33, 2036 (1900)) whose conclusions concerning them differed from those reached by Plöchl.

** It is interesting to note that no references to this compound appear in Beilstein's "Handbuch der organischen Chemie" or in Chemical Abstracts.

(23) Erlenmeyer, Jr., Ann., 275, 1 (1893); Ber., 33, 2036 (1900); Ann., 337, 265 (1904).

product. He formulated the reactions in the following manner:



The anhydride proved to be 2-phenyl-4-benzaloxazolone (V), and Erlenmeyer introduced the general name "azlactone"* for this type of substance. In order to effect the condensation between benzaldehyde and hippuric acid, it is necessary to carry out the reaction in the presence of acetic anhydride and sodium acetate. The reaction is a fairly rapid one[24], and as soon as (IV) is formed, it is dehydrated by the acetic anhydride to (V).

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* Azlactones have been shown to be very useful intermediates for the preparation of arylpyruvic acids, β-arylalanines, and N-methyl-derivatives of the latter compounds. See Johnson, Organic Reactions, Vol. 1, p. 231, and Carter, ibid, Vol. 3, pp. 198-240.

(24) Erlenmeyer, Ann., 271, 137 (164) (1892).

Upon further hydrolysis of (IV), Plöchl obtained benzoic acid, ammonia and a nitrogen-free acid, which he claimed was phenylglycidic acid. The latter acid melted at 154-155°, with evolution of carbon dioxide, and produced a deep green color when an alcoholic solution of the acid was treated with ferric chloride.

Plöchl maintained that his acid was the true phenylglycidic acid, and that the so-called phenylglycidic acid, which Glaser[18] had prepared by the reaction between either phenylchloro- or phenylbromolactic acids and alcoholic potassium hydroxide, must have been some other substance.

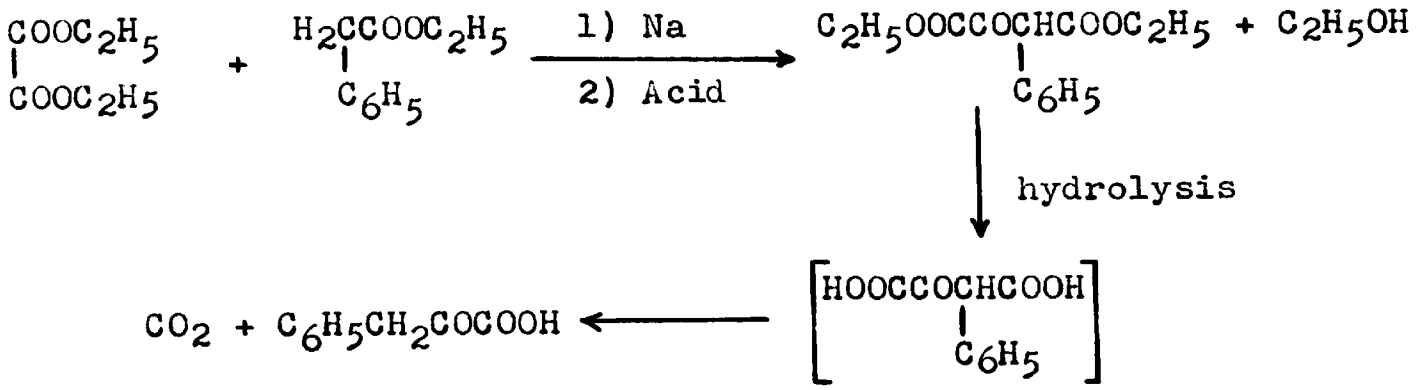
Three years later Erlenmeyer[25] announced, in a preliminary report, that he had noticed some indications of the presence of a ketone group in Plöchl's acid, and that he intended to study the problem more completely. Thereupon, Plöchl[26] put forth additional arguments to show that his acid could not possibly be a ketonic acid.

Wislicensus[27], who was interested in the condensation of unlike esters, by means of sodium, described the condensation of ethyl oxalate and ethyl phenylacetate as an example of this condensation because of the debate between Plöchl and Erlenmeyer. The ester, which Wislicensus obtained from the condensation, hydrolyzed with carbon dioxide evolution,

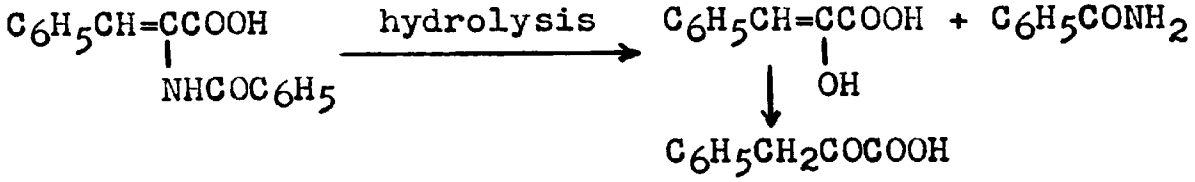
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(25) Erlenmeyer, Ber., 19, 2576 (1886).
(26) Plöchl, Ber., 19, 3167 (1886).
(27) Wislicensus, Ber., 20, 589 (1887).

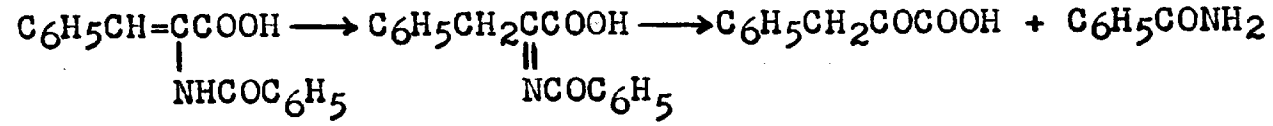
and yielded phenylpyruvic acid. He found that this acid was identical with Plöchl's phenylglycidic acid.



In 1892, Erlenmeyer[24] published a long article in which he demonstrated that Glaser's acid was the true phenylglycidic acid and that the acid described by Plöchl was the isomeric phenylpyruvic acid. Erlenmeyer illustrated the formation of phenylpyruvic acid by hydrolysis of α-(benzoylamino)-cinnamic acid (IV) in the following manner:



However, the hydrolysis of (IV) to the pyruvic acid is more easily understood if it is assumed that it is the imino form of (IV) which undergoes hydrolysis:



Erlenmeyer stated that the sodium salt of phenylglycidic acid, prepared by Glaser's method, reacted with hydrogen

chloride to form β-chloro-β-phenyllactic acid, and with ammonia to produce an amino acid. He mentioned that the latter acid must have been α-hydroxy-β-aminopropionic acid provided that the ammonia had reacted with phenylglycidic acid in the same manner that it reacts with glycidic acid. Piperidine and aniline reacted in a manner similar to that of ammonia.

Since phenylglycidic acid contains two unlike asymmetric carbon atoms, it should be capable of existence in two racemic forms. Erlenmeyer was able to obtain a dextro- and levorotatory sodium phenylglycidate.

Erlenmeyer synthesized phenylglycidic acid, in the form of its ethyl ester, by a new procedure, namely, by interaction of benzaldehyde and ethyl chloroacetate in the presence of sodium ethylate*.

In conformity with its structure as a keto acid, Erlenmeyer found that Plöchl's acid formed a phenylhydrazone, an oxime and, when treated with 1,2-diaminotoluene, a quinoxaline. The oxime, on reduction, was converted into phenylalanine.

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* Although Erlenmeyer was the first investigator to describe a reaction of this type, Darzens, at a later date, made an extensive study of the condensation of ketones with esters of α-chloro acids, and the general reaction has become known as the Darzens glycidic ester condensation.

$$C_6H_5CH_2C(=NOH)COOH \xrightarrow{2H_2} C_6H_5CH_2CH(NH_2)COOH + H_2O$$

Erlenmeyer showed also that the phenylpyruvic acid, which he had synthesized by the process outlined below, was the same acid as that obtained by Plöchl.

$$C_2H_5OOCCOOC_2H_5 + \underset{\underset{C_6H_5}{|}}{CH_2CN} \xrightarrow{C_2H_5ONa} C_2H_5OOCCOCHCN \quad (C_6H_5 \text{ on } CHCN)$$

$$\downarrow \text{hydrolysis}$$

$$HOOCCOCHCN \quad (C_6H_5 \text{ on } CHCN)$$

$$C_6H_5CH_2COCOOH + NH_3 + CO_2 \leftarrow$$

The synthesis of phenylpyruvic acid by both Erlenmeyer's and Plöchl's methods has recently been repeated by Hurd and Raterink[28]*, who reported that both methods are tedious

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(28) Hurd and Raterink, J. Am. Chem. Soc., 56, 1348 (1934).

* Hopkins and Chisholm (Can. J. Res., 24, 89 (1946)) prepared phenylpyruvic acid by means of the following reactions, and stated that their method may be more convenient than those used by Hurd and Raterink.

$$C_6H_5CH=C(CN)COOH \xrightarrow{NaOCl} C_6H_5CH(OH)C(OH)(CN)COOH$$

$$\downarrow 52\% \text{ HBr}$$

$$C_6H_5CH_2COCOOH$$

It was assumed by the authors that phenylglyceric acid and phenylglycidic acid were intermediates in the last step of the synthesis.

and that Erlenmeyer's method yielded an acid which melted at 146-147° rather than 155°.

In a German patent Erdmann[29] claimed that, when cinnamic acid was treated with alkaline hypobromite, a β-lactone of glyceric acid, $C_6H_5\underset{\text{O}}{\text{CHCH(OH)CO}}$ (m.p. 83-84°), was obtained. He then stated, in another patent[30], that the lactone, when heated or heated in the presence of water, decomposed quantitatively into phenylacetaldehyde and carbon dioxide. Phenylacetaldehyde is an important substance in the perfume industry, and Erdmann mentioned that it is advantageous to obtain it from his β-lactone; when the aldehyde is prepared from phenylglycidic acid, a considerable amount of phenylglyceric acid is produced[31].

$$C_6H_5CH\text{-}CHCOOH \xrightarrow[H_2O]{\text{heat}} C_6H_5CH_2CHO + CO_2 + C_6H_5CH(OH)CH(OH)COOH$$

Interaction of cinnamic acid and hypobromous acid yields α-bromo-β-hydroxy-β-phenylpropionic acid; by the use of hypochlorous acid, the corresponding α-chloropropionic acid is

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(29) Erdmann, German Patent, 107,228 (1899); Frdl., 5, 881.
(30) Erdmann, German Patent, 107,229 (1899); Frdl., 5, 882.
(31) Lipp, Ber., 16, 1286 (1883).

obtained*. Dieckmann(32) found that these halopropionic acids, when treated with alkali, were converted into phenylglycidic acid (m.p. 83-84°). The phenylglycidic acid, which he obtained from the propionic acids, and also by hydrolysis of the ethyl ester of phenylglycidic acid**, proved to be identical with Erdmann's "β-lactone of phenylglyceric acid", so the latter substance was really the glycidic acid.

Phenylglycidic acid has also been prepared by the oxidation of cinnamaldehyde by means of either alkaline hydrogen peroxide or hypohalites(33).

Diphenylglycidic Acids

β,β-Diphenylglycidic Acid.

It was found by Darzens(34) that a great variety of ketones can be condensed with ethyl chloroacetate, with the

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* Berner and Riiber (Ber., 54, 1945 (1921)) found this to be the case with hypochlorous acid; similarly, Farmer and Hose (J. Chem. Soc., 962 (1933)) stated that the direct addition of hypochlorous acid to cinnamic acid yields only the α-chlorohydrin acid.

(32) Dieckmann, Ber., 43, 1035 (1910).

** Prepared by Dieckmann, according to Erlenmeyer's procedure(24), from benzaldehyde, ethyl chloroacetate and sodium ethylate.

(33) Kaufmann, French Patent, 682,471; Chem. Abst., 24, 4306 (1930).

(34) Darzens, Compt. rend., 139, 1214 (1904); ibid., 141, 766 (1905); ibid., 142, 214 (1906).

aid of powdered sodium ethylate as the condensing agent, to form epoxy compounds. The reaction has become known as the Darzens glycidic ester condensation.

Erlenmeyer[24] was the first to postulate a mechanism for the Darzens condensation when he stated that benzaldehyde, in the presence of sodium ethylate, reacted with ethyl chloroacetate in the following manner:

$$C_6H_5CHO + NaOC_2H_5 \longrightarrow C_6H_5CH(ONa)OC_2H_5$$

$$C_6H_5CH(ONa)OC_2H_5 + CH_2ClCOOC_2H_5 \longrightarrow C_6H_5CH(ONa)CH(Cl)COOC_2H_5$$

$$C_6H_5CH(ONa)CH(Cl)COOC_2H_5 \longrightarrow C_6H_5\underset{\diagdown\,O\,\diagup}{CH\text{-}CHCOOC_2H_5} + NaCl$$

Claisen[35] assumed that an analogous reaction occurred when acetophenone was condensed with ethyl chloroacetate in the presence of sodamide:

$$C_6H_5COCH_3 + NaNH_2 \longrightarrow C_6H_5\underset{\displaystyle CH_3}{\overset{\displaystyle |}{C}}(ONa)NH_2$$

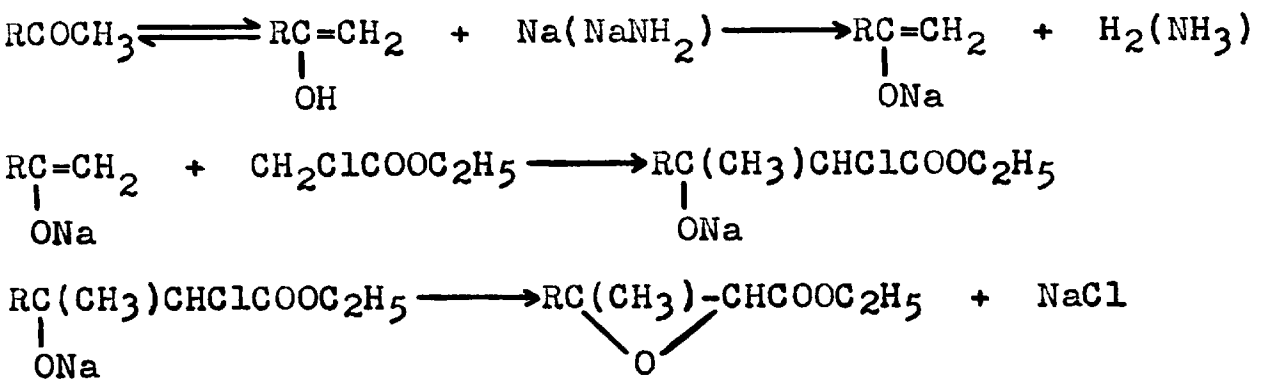
$$C_6H_5\underset{\displaystyle CH_3}{\overset{\displaystyle |}{C}}(ONa)NH_2 + CH_2ClCOOC_2H_5 \longrightarrow C_6H_5\underset{\displaystyle CH_3}{\overset{\displaystyle |}{C}}(ONa)CHClCOOC_2H_5$$

$$C_6H_5\underset{\displaystyle CH_3}{\overset{\displaystyle |}{C}}(ONa)CHClCOOC_2H_5 \longrightarrow C_6H_5\underset{\diagdown\,O\,\diagup}{C(CH_3)\text{-}CHCOOC_2H_5} + NaCl$$

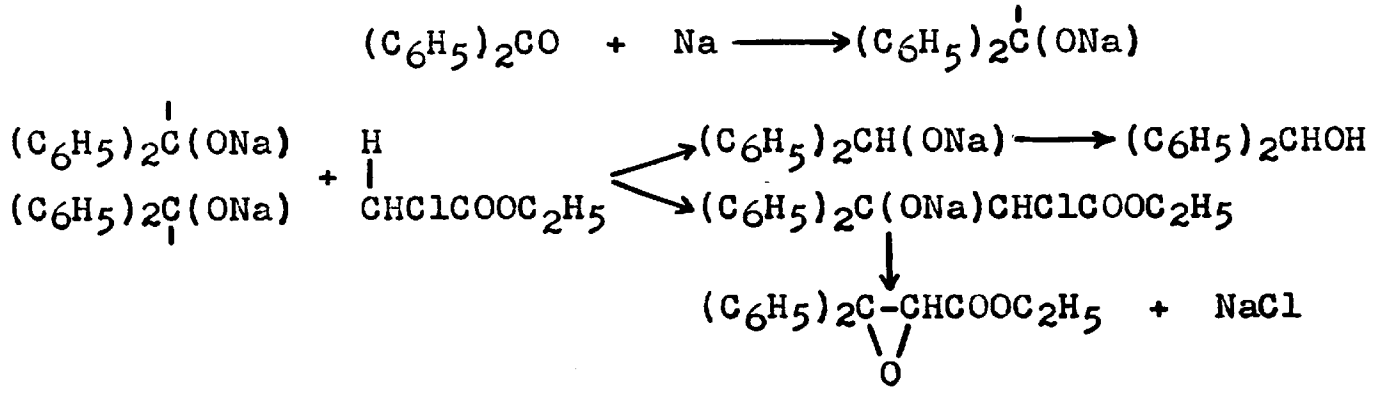
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(35) Claisen, Ber., 38, 693 (699) (1905).

Rutowski and Dajew[36] believed that the enol forms of aliphatic aldehydes and ketones react with either sodium or sodamide to form sodium enolates, which then condense with the chloro ester as follows:



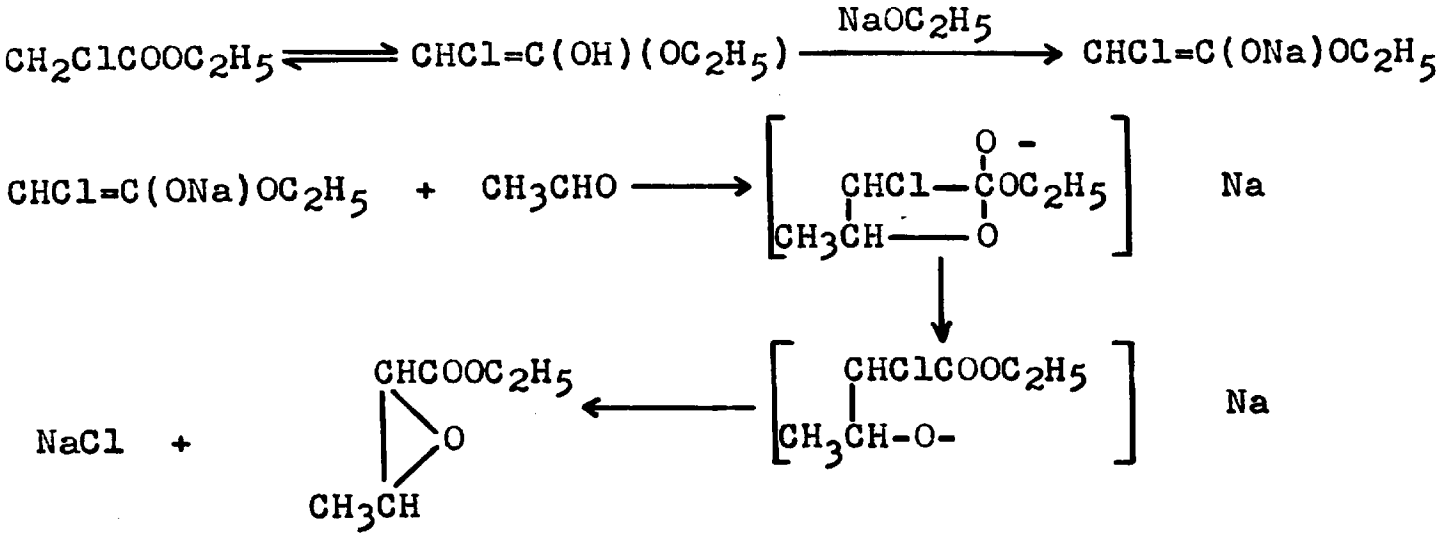
They proposed a different mechanism for aromatic aldehydes and ketones, which are not capable of enolization. According to them, sodium reacts with such carbonyl compounds to form sodium derivatives, which then condense with ethyl chloroacetate. This mechanism involves free radical formation, and is exemplified by the use of benzophenone in the following scheme:



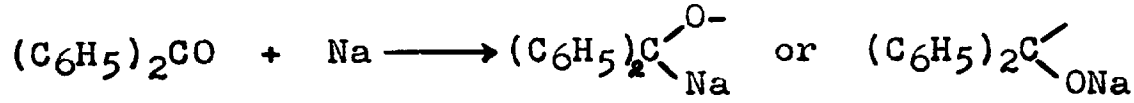
(36) Rutowski and Dajew, Ber., 64, 693 (1931).

This mechanism enabled them to account for the formation of an equivalent amount of benzhydrol, which they had isolated from the reaction mixture.

The formation of the enolate of the halo ester was first suggested by Scheibler and Tutundzitsch[37], who offered the following scheme as a possible mechanism for the reaction:



Fourneau and Billeter[6] devised an even more complicated mechanism to explain the behavior of benzophenone in the condensation. According to these investigators, sodium may add to benzophenone in two ways:



They preferred the latter formula, and stated that two molecules of this free radical combined to form a disodium compound which

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(37) Scheibler and Tutundzitsch, Ber., 64, 2916 (1931).

then reacted with ethyl chloroacetate.

$$2\ (C_6H_5)_2\dot{C}(ONa) \longrightarrow (C_6H_5)_2C(ONa)(NaO)C(C_6H_5)_2$$

$$(C_6H_5)_2C(ONa)(NaO)C(C_6H_5)_2 \xrightarrow{2\ CH_2ClCOOC_2H_5} 2\ (C_6H_5)_2C(ONa)CHClCOOC_2H_5 + H_2$$

$$(C_6H_5)_2C(ONa)CHClCOOC_2H_5 \longrightarrow (C_6H_5)_2C(O)CHCOOC_2H_5$$

In order to explain how Rutowski and Dajew[36] obtained benzhydrol from this reaction, Fourneau and Billeter postulated that the disodium compound might also react with the chloro ester as follows:

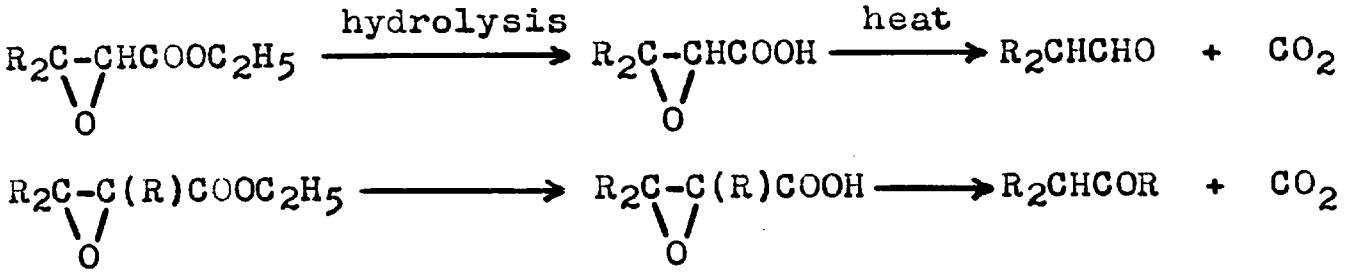
$$\begin{matrix}(C_6H_5)_2C(ONa) \\ (C_6H_5)_2C(ONa)\end{matrix} + \begin{matrix}CHClCOOC_2H_5 \\ H\end{matrix} \longrightarrow \begin{cases}(C_6H_5)_2C(ONa)CHClCOOC_2H_5 \\ (C_6H_5)_2CH(ONa) \longrightarrow (C_6H_5)_2CHOH\end{cases}$$

Several of these investigators[35,36,37] reported that, when benzaldehyde was employed in the condensation, some ethyl α-chlorocinnamate was formed in addition to the glycidic ester. It was generally agreed that the cinnamic ester originated in the following manner:

$$C_6H_5CH(ONa)CH(Cl)COOC_2H_5 \longrightarrow C_6H_5CH{=}C(Cl)COOC_2H_5 + NaOH$$

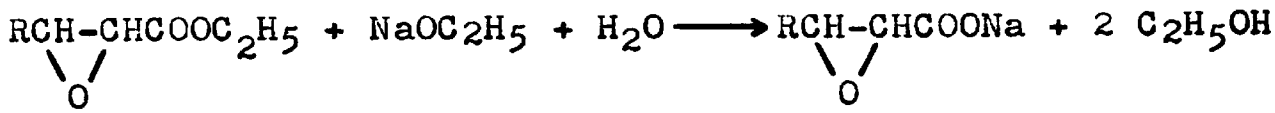
It may be seen from the above discussion that there is little agreement regarding the manner in which the condensation actually takes place.

The importance of epoxy esters lies especially in the fact that they can be converted very easily into aldehydes or ketones and, in some instances, this process represents the most practical method for the preparation of the latter substances. The process involves the hydrolysis of the esters, followed by the thermal decomposition of the resulting acids.



As far as we are aware, no mechanism for the thermal decomposition of the glycidic acids has ever been postulated.

Claisen[35] found that sodamide served well as the condensing agent in the Darzens condensation. He also devised a method for the hydrolysis of glycidic esters in which a cold, alcoholic solution of the ester was treated with a mixture of one equivalent of sodium ethylate and one equivalent of water.



In most cases when Claisen's procedure is used, the sodium salt of the acid separates as a solid from the cold solution within a short time, and may be purified by subsequent washing

with cold alcohol and ether. The method finds wide application in the hydrolysis of esters of glycidic acids.

Pointet[38] was the first to use benzophenone in the Darzens condensation, and did so in an effort to prepare diphenylacetaldehyde. By the use of sodium ethylate as the condensing agent, he obtained an ester, b.p. 202-204° (12 mm.), which melted at 47°. He believed this ester to be the desired ethyl β,β-diphenylglycidate. The ester was hydrolyzed by the method of Claisen, and the resulting sodium salt of the acid was treated with the calculated amount of sulfuric acid in aqueous solution in order to liberate the free acid. Pointet did not describe his acid, but directly heated the acidic, aqueous solution on a water-bath in order to convert the acid into carbon dioxide and diphenylacetaldehyde. However, no gas evolution was noted until the acid had been isolated and distilled; the distillate proved to be diphenylacetic acid rather than diphenylacetaldehyde. Although Pointet altered many of the conditions of the condensation, the ultimate product was always diphenylacetic acid. Similar results were obtained when substituted benzophenones were used in the condensation; the ultimate products were the corresponding diphenylacetic acids rather than the expected aldehydes.

Since it is now known that thermal decomposition of β,β-diphenylglycidic acid produces diphenylacetaldehyde in good yield, and that diphenylpyruvic acid, when heated, is converted into diphenylacetic acid, Pointet's results can

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(38) Pointet, Compt. rend., 148, 417 (1909).

be explained by the assumption that he actually heated diphenylpyruvic acid instead of diphenylglycidic acid[39].

$$(C_6H_5)_2C\text{-}CHCOOH \xrightarrow{\text{heat}} (C_6H_5)_2CHCHO + CO_2$$

$$(C_6H_5)_2CHCOCOOH \longrightarrow (C_6H_5)_2CHCOOH + CO + \text{other products}$$

From his results, Pointet concluded that the aldehyde synthesis described by Darzens was not a general one, and cited his substituted glycidic acids as compounds which behave in an exceptional manner.

No further work on the Darzens condensation, using benzophenone, was done until 1928 when Troell[39] stated that he prepared ethyl β,β-diphenylglycidate as an intermediate in a study of hydroxy-chloroacids. He omitted the details of the preparation of his ester except to say that Claisen's directions were followed. According to Troell, sodamide gave higher yields of the ester than sodium ethylate. His product, which he could never obtain in solid form, boiled at 202° (12 mm.). Hydrolysis of the distilled ester yielded the sodium salt of an acid from which the free acid was liberated with hydrogen chloride. The chlorine-free acid melted at 116°, and its properties led Troell to conclude that he had isolated diphenylpyruvic acid, $(C_6H_5)_2CHCOCOOH$*, instead

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(39) Troell, Ber., 61, 2497 (1928).

* Another compound, also called diphenylpyruvic acid, has been reported by Hemmerle (Compt. rend., 162, 758 (1916)). This investigator stated that two molecules of phenylpyruvic acid combined to form a compound, m.p. 194° (dec.), which he called diphenylpyruvic acid.

$$2\ C_6H_5CH_2COCOOH \longrightarrow C_6H_5CH_2C(OH)COOH$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad |$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad C_6H_5CHCOCOOH$$

of β,β-diphenylglycidic acid. He claimed that he had obtained ethyl β,β-diphenylglycidate as a condensation product but that, during the distillation of the ester, it rearranged into ethyl diphenylpyruvate.

Troell found that, in aqueous solution, the acid exhibited greater stability than could be expected of a glycidic acid. In contrast to a glycidic acid, the acid or its sodium salt reacted with phenylhydrazine to form a phenylhydrazone, m.p. 189° (dec.)* and was converted by heat into diphenylacetic acid.

Rutowski and Dajew[36] reacted ethyl chloroacetate with the monosodium derivative of benzophenone. The product was fractionated to give benzhydrol and a good yield of an ester which, after it had been distilled at 210-225° (25 mm.), melted at 47°‡. Pointet[38] had stated previously that ethyl β,β-diphenylglycidate melts at 47°. Rutowski and Dajew

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* Hydrolysis of the crude ester yielded the sodium salt of an acid (sodium β,β-diphenylglycidate) which did not form a phenylhydrazone.

‡ Rutowski and Dajew mentioned that their ester, when dissolved in acetic acid and treated with potassium iodide, gave a positive test for an "oxyd" (epoxy) group. Darzens (Compt. rend., 150, 1243 (1910)) had stated previously that ethyl β,β-dimethylglycidate, when treated with anhydrous hydriodic acid in ether solution, produced free iodine.

$$(CH_3)_2C\underset{\backslash\,/}{-}CHCOOC_2H_5 \;+\; 2\,HI \longrightarrow (CH_3)_2C{=}CHCOOC_2H_5 \;+\; H_2O \;+\; I_2$$
$$\qquad\qquad O$$

See also Bodforss, Ber., 49, 2795 (2801) (1916).

hydrolyzed their ester in an undisclosed manner and obtained an acid, m.p. 114-115°, which they stated was β,β-diphenylglycidic acid.

Assuming that Pointet, as well as Rutowski and Dajew, actually had the glycidic ester* it is strange that the corresponding acids which they obtained by hydrolysis had the properties of the pyruvic acid. It is possible that rearrangement from the epoxy to the keto structure could have occurred during the liberation of the acids from their sodium salts. Erlenmeyer(40) noted that the sodium salt of phenylglycidic acid was rearranged, in part, to phenylpyruvic acid on treatment with hot hydrochloric acid.

$$C_6H_5CH\text{-}CHCOONa \xrightarrow[HCl]{\text{hot, aq.}} C_6H_5CH_2COCOOH + C_6H_5CH_2CHO + C_6H_5CH(OH)CH(OH)COOH$$

Kohler, Richtmyer and Hester(41) condensed ethyl chloroacetate and benzophenone by means of sodium ethylate. They preferred the use of sodium ethylate since they claimed that the acid amides, produced by the use of sodamide, complicated the isolation of pure substances from the reaction mixture. According to these investigators, the product of the condensation was ethyl β,β-diphenylglycidate which they were unable to isolate in the pure state because "it could not be separated from the unreacted benzophenone and vacuum

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* It was shown by us that the true glycidic ester melted at 48-49°.

(40) Erlenmeyer, Ber., 33, 3001 (1890).
(41) Kohler, Richtmyer and Hester, J. Am. Chem. Soc., 53, 205 (1931).

distillation converted it into the isomeric ketonic ester, ethyl diphenylpyruvate". The yield of the glycidic ester from the condensation was stated to be 75%, and was determined indirectly by its conversion to ethyl β,β-diphenylglycerate by means of steam distillation of the crude product. The glyceric ester was a solid compound, and its quantitative estimation presented no difficulty.

$$(C_6H_5)_2C\underset{\backslash\,/}{-}CHCOOC_2H_5 \xrightarrow[\text{distillation}]{\text{steam}} (C_6H_5)_2C(OH)CH(OH)COOC_2H_5$$
$$\qquad\quad O$$

The distilled ester, as obtained by these workers, boiled at 190° (3-10 mm.) and melted at 37°*. They pointed out that the melting point of their ester did not agree with the value (47°) reported by Pointet(38), and explained the discrepancy by stating that "either Pointet's melting point was a typographical error or, as Troell suggests, his compound was benzophenone". No mention was made by them of the melting point of 47° reported for this ester by Rutowski and Dajew**.

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* In order to obtain the ester in crystalline form, Kohler and his co-workers found it necessary to prepare a sample of it from the reaction between the silver salt of the corresponding acid and ethyl iodide. This procedure provided a sample of the ester which solidified, and was used as seed crystals.

** Since the papers of Rutowski and Dajew and of Kohler, Richtmyer and Hester appeared in the same year, it is possible that the paper of Rutowski and Dajew was not available to Kohler and his associates.

As has been stated, Kohler and his co-workers were of the opinion that transformation of the glycidic ester to the pyruvic ester occurred during distillation, and they submitted the following reactions and properties of the distilled ester as evidence for this belief.

1). It gave no glyceric ester upon distillation with steam.

2). Diphenylacetic acid was produced when the ester was treated with alkaline hydrogen peroxide.

3). Alkaline hydrolysis gave an acid, m.p. 116°, which was diphenylpyruvic acid. The phenylhydrazone of this acid melted at 210° or 245° depending upon the rate of heating. The authors pointed out that Troell[39] had reported the melting point of this derivative to be 189° (dec.).

4). The phenylhydrazone of the ester melted at 99-100°.

5). Ethyl α,β,β-triphenyllactate was formed by the reaction between the ester and phenylmagnesium bromide.

These investigators also found that methyl β,β-diphenylglycidate, prepared from methyl chloroacetate in the same manner as the ethyl ester, likewise rearranged during distillation to the isomeric methyl diphenylpyruvate, b.p. 175° (5 mm.); m.p. 75°.

Berger[42] stated also that rearrangement of the glycidic ester occurred during its distillation. By the use of sodamide as the condensing agent, he obtained an ester,

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(42) Berger, J. prakt. Chem., (2) 152, 267 (283) (1939).

b.p. 202° (14 mm.), which he maintained was ethyl diphenylpyruvate. Hydrolysis of the ester by the method of Claisen, and subsequent acidification of the resulting sodium salt, yielded an acid, the properties of which he did not describe, except to say that it was recrystallized from water. Being primarily interested in hydrazino-acids, he reacted his acid directly with hydrazine hydrate and obtained the hydrazone, m.p. 137°, which was reduced to the hydrazino-acid, m.p. 182-194°. The fact that these derivatives were formed served as the basis for his assertion that the distilled ester contained a keto group, i.e., that it was the pyruvic ester.

Milas and co-workers(43) regarded the glycidic ester, obtained from β-ionone and ethyl chloroacetate, as being a mixture of esters: the epoxy, the keto and the enol form of the keto ester. This assumption enabled them to account, at least partially, for the formation of several products when the hydrolyzed crude ester was decarboxylated.

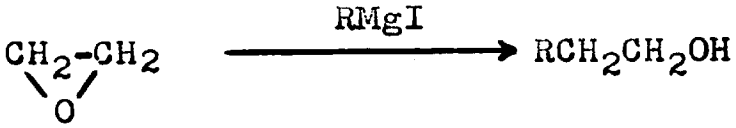
Four other references to ethyl β,β-diphenylglycidate are found in the literature in connection with its behavior toward Grignard reagents and reduction. According to Bardon and Ramart(44), when an excess of methylmagnesium iodide was reacted with ethyl β,β-diphenylglycidate*, either in the

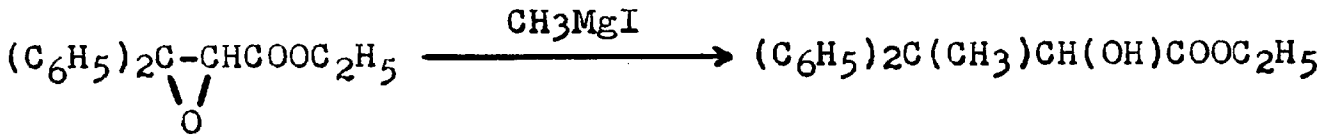
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(43) Milas, Lee, Sakal, Wohlers, MacDonald, Grossi and Wright, J. Am. Chem. Soc., 70, 1584 (1948).
(44) Bardon and Ramart, Compt. rend., 183, 214 (1926).

* The investigators did not mention the source or the properties of their initial ester.

cold or at the reflux temperature of ether, an ester was produced which, upon hydrolysis, yielded β-methyl-β,β-diphenyllactic acid. Thus, they assumed that the Grignard reagent reacted with the epoxy group of the ester in the same manner as it does with ethylene oxide(45).





This postulation was based on the fact that the properties of the acid, which they obtained, differed from those of the isomeric β-hydroxy acid as described by Rupe, Stieger and Fiedler(46). They did not consider that their initial ester might have been ethyl diphenylpyruvate as the literature, as well as our results, later indicated.

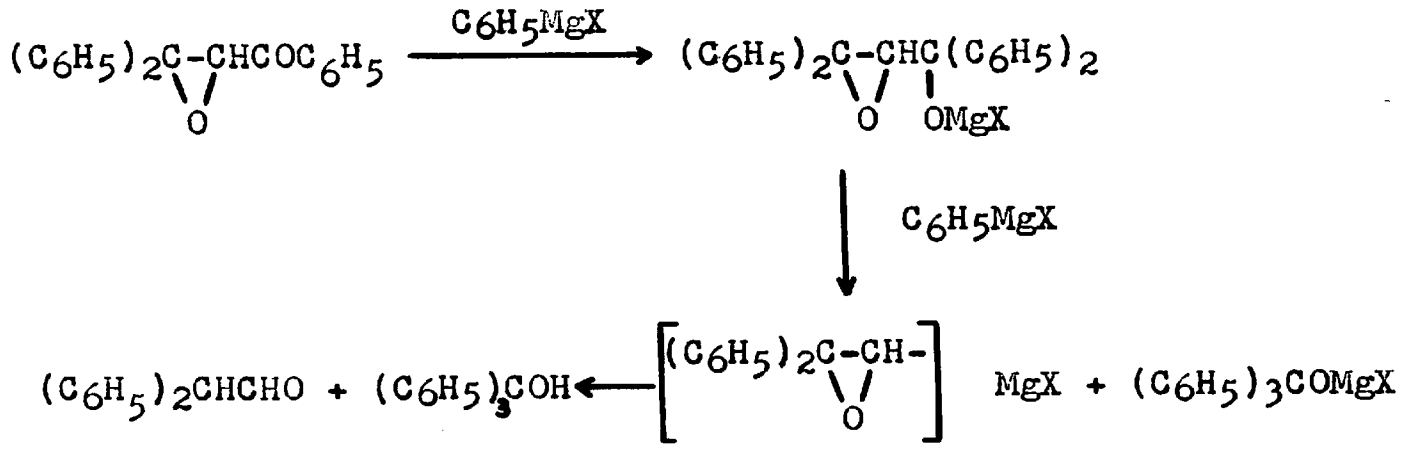
Bardon and Ramart also treated their glycidic ester with phenylmagnesium bromide, but they failed to identify the products beyond stating that one of the products was an ester-alcohol. The senior author(47) remarked, in a later publication, that the identities of these compounds had not yet been determined.

It was found later by Kohler and his associates(41) that α,β-epoxy carbonyl compounds react differently toward

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(45) Grignard, Compt. rend., 136, 1260 (1903).
(46) Rupe, Stieger and Fiedler, Ber., 47, 63 (1914).
(47) Billon-Bardon, Compt. rend., 188, 1412 (1929).

an excess of a Grignard reagent than does ethylene oxide. In working with epoxy ketones, they established that the Grignard reagent causes cleavage of the epoxy compound, and that one of the products is always a tertiary alcohol. The mechanism of this cleavage, as postulated by these investigators, is as follows:



This reaction was extended to the α,β-epoxy ester, ethyl β,β-diphenylglycidate*, and the products were stated to be diphenylacetaldehyde, biphenyl and triphenylcarbinol. On the basis of these results, the authors stated that the glycidic ester was cleaved in the manner to be expected, and that the products obtained by Bardon and Ramart[44] from this reaction were derived from the ketonic ester rather than from the glycidic ester.

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* Since these investigators were unable to isolate the glycidic ester in the pure state, claiming that distillation converted it to the isomeric pyruvic ester, this reaction was run on crude ester, which was actually a mixture of the ester, benzophenone and ethyl chloroacetate.

Kohler and his associates also treated ethyl diphenylpyruvate with an excess of phenylmagnesium bromide and, depending on the conditions under which the reaction was carried out, their products were those to be expected: $(C_6H_5)_2CHC(OH)(C_6H_5)COOC_2H_5$, $(C_6H_5)_2CHC(OH)(C_6H_5)COC_6H_5$ and $(C_6H_5)_2CHC(OH)(C_6H_5)C(OH)(C_6H_5)_2$. The properties of these compounds did not show good agreement with those of the products obtained from the reaction described by Bardon and Ramart.

Darzens[48] failed to isolate and separate the products formed when ethyl β,β-dimethylglycidate was treated with common Grignard reagents. However, when the ester was reacted with methyl iodide in the presence of a zinc-copper alloy, an excellent yield of ethyl α,β,β-trimethyllactate was obtained. His explanation for this peculiar behavior was that the glycidic ester was rearranged by the organo-zinc derivative to the isomeric keto ester, the carbonyl group of which then reacted with the methyl-zinc iodide in the usual manner.

According to Billon-Bardon[47], reduction of ethyl β,β-diphenylglycidate with sodium and alcohol gave a 60% yield of β,β-diphenyllactic acid in addition to other distillable products, which were not identified. Mme. Billon-Bardon accounted for the formation of this acid by assuming that the epoxy ring was opened to form the sodium alcoholate

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(48) Darzens, Compt. rend., 152, 443 (1911).

of the α-hydroxy ester, which was immediately hydrolyzed to the corresponding acid. Again, it is possible that her initial ester could have been ethyl diphenylpyruvate, the reduction of which would give the same product.

$$(C_6H_5)_2\underset{\diagdown O \diagup}{C\text{-}CHCOOC_2H_5} \xrightarrow[C_2H_5OH]{Na} (C_6H_5)_2CHCH(ONa)COONa$$

$$(C_6H_5)_2CHCOCOOC_2H_5 \xrightarrow[C_2H_5OH]{Na} (C_6H_5)_2CHCH(OH)COOH$$

Entirely different results were obtained by Verley[49] when he reduced glycidic esters with sodium and alcohol. According to him, the reduction proceeds as follows:

$$RCH\underset{\diagdown O \diagup}{\text{-}CHCOOC_2H_5} + 4\ Na \xrightarrow[\text{reflux}]{\text{alcohol}} RCH_2CH_2CH_2OH + RCH_2CH_2COOH$$

The reaction was presented as a general one for the preparation of alcohols and acids, which are formed in equivalent amounts and in good yield. Ethyl β,β-diphenylglycidate, however, was not included as an example of a glycidic ester reduced in this manner.

The disagreement in the literature regarding ethyl β,β-diphenylglycidate and the isomeric ketonic ester may be summarized as follows:

1). Two investigators[36,38] found that the Darzens condensation yielded an ester, which, after purification by distillation and recrystallization, melted at 47°.

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(49) Verley, Bull. soc. chim., (4) 35, 487 (1924).

2). One of these investigators[36] reported that the corresponding acid melted at 116°, and claimed it to be the glycidic acid. The other worker[38] did not describe his glycidic acid, but noted that its thermal decomposition product was diphenylacetic acid rather than diphenylacetaldehyde.

3). Other investigators[39,41,42] maintained that, although the primary product of the condensation was the glycidic ester, distillation caused its rearrangement to the isomeric pyruvic ester. One of these workers[41] obtained the pyruvic ester as a solid, m.p. 37°.

4). Hydrolysis of the distilled ester yielded an acid, m.p. 116°, which was shown by its reactions to be the pyruvic acid.

From these results it appears that two apparently different esters having approximately the same boiling point but different melting points yield the same acid upon hydrolysis, and this acid is diphenylpyruvic acid.

The following table also shows the different melting and boiling points reported by different investigators for β,β-diphenylglycidic and diphenylpyruvic acids and their derivatives. Data determined during this investigation have been included.

TABLE I

β,β-Diphenylglycidic and Diphenylpyruvic Acids and their Derivatives

	Ester[a]				Acid		
Investigator	B.p., °C.	M.p., °C.	Reported Structure	Phenylhydrazone M.p., °C.	M.p., °C.	Reported Structure	Phenylhydrazone, M.p., °C.
Pointet[38]	202-4 (12 mm.)	47	Glycidic	---	---	---	---
Troell[39]	202 (12 mm.)	oil	Pyruvic	---[b]	116	Pyruvic	189 (dec.)
Rutowski and Dajew[36]	210-15 (25 mm.)	47	Glycidic	---	114-5	Glycidic	---
Kohler et al.[41]	190 (3-10 mm.)	37	Pyruvic	99-100	116	Pyruvic	210, 245[c]
Berger[42]	202 (14 mm.)	oil	Pyruvic	---	---	Pyruvic	---[d]
Faust	152-3 (1 mm.)	48-9	Glycidic	---	71 (dec.)	Glycidic[e]	---
*	* *						
Faust	152-5 (1 mm.)	37[f]	Pyruvic	101-2	116-7	Pyruvic[e]	208 (dec.)

(a) All investigators, who condensed benzophenone with ethyl chloroacetate, agreed that ethyl β,β-diphenylglycidate was produced, but some of them maintained that, during the distillation of the ester, it rearranged into the isomeric ethyl diphenylpyruvate.
(b) Troell reported that, prior to distillation, his ester could not be converted into a phenylhydrazone.
(c) The melting point of this compound was reported to depend upon the rate of heating.
(d) Berger prepared the hydrazone of his acid and reported it to melt at 137°.
(e) We prepared the acid amides of the glycidic and the pyruvic acids which were unknown hitherto. The glycidic acid amide melted at 148-149°; the pyruvic acid amide melted at 167-168°.
(f) This material, the pyruvic ester, was prepared from the glycidic ester by heating the latter in the presence of an acid.

α,β-Diphenylglycidic Acid.

The only reference in the literature to α,β-diphenylglycidic acid seems to be that of Kohler and Brown[50]. These investigators obtained two isomeric forms of the acid in connection with a study of the reaction between desyl chloride, $C_6H_5COCH(Cl)C_6H_5$, and methanolic potassium cyanide. According to them, the products from the reaction consisted of two isomeric glycidonitriles, and the respective imino ethers of these nitriles:

$$C_6H_5COCH(Cl)C_6H_5 + KCN + CH_3OH \longrightarrow C_6H_5CH\text{-}C(CN)C_6H_5 + \text{(epoxide)}$$

$$C_6H_5CH\text{-}C(C_6H_5)C(=NH)OCH_3 \text{ (epoxide)}$$

Treatment of the imino ethers with water yielded two forms of the methyl esters, which were then hydrolyzed to the corresponding acids.

$$C_6H_5CH\text{-}C(C_6H_5)C(=NH)OCH_3 \text{ (epoxide)} \longrightarrow C_6H_5CH\text{-}C(C_6H_5)COOCH_3 \text{ (epoxide)}$$

$$\downarrow \text{ hydrolysis}$$

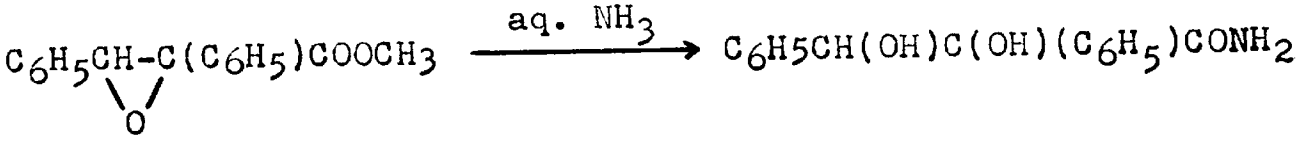
$$C_6H_5CH\text{-}C(C_6H_5)COOH \text{ (epoxide)}$$

The two forms of the acid were reported to melt at 90° and 121°, and the higher melting form was obtained from the higher

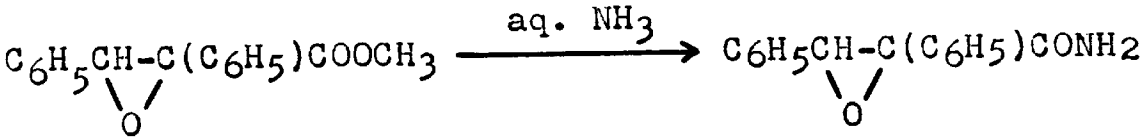
(50) Kohler and Brown, J. Am. Chem. Soc., 55, 4299 (1933).

melting form of the corresponding methyl ester.

The authors also stated that the higher melting form of the methyl ester was converted, by the action of aqueous ammonia, into the corresponding glyceramide; m.p. 135°*.



However, the lower melting form of the methyl ester was allegedly converted into the corresponding glycidamide, m.p. 205°⁂, by the same treatment.



α-Methyl-β-phenylglycidic Acid.

As far as we are aware, α-methyl-β-phenylglycidic acid has not been described hitherto. We prepared and obtained this acid for the preparation of β-diethylaminoethyl α-methyl-β-phenylglycidate hydrochloride. Ethyl α-methyl-β-phenylglycidate has been described by Darzens(51), who prepared it by

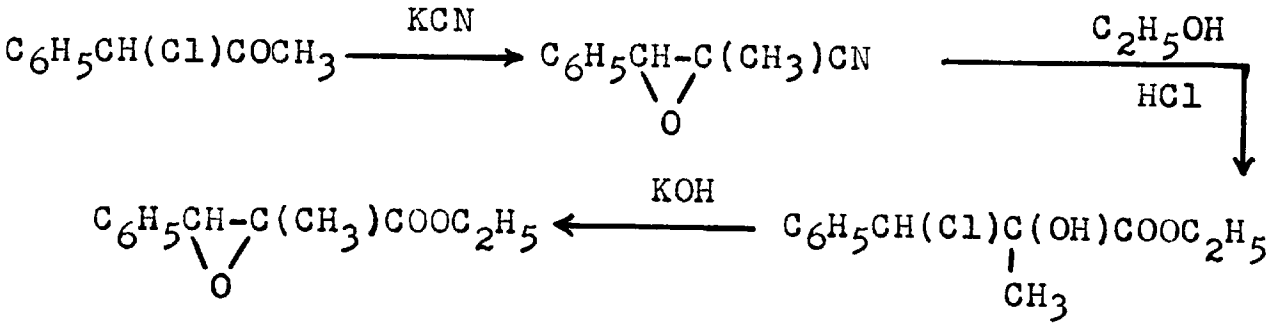
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* The isomeric glyceramide was reported by these investigators to melt at 235°.

⁂ This amide was prepared, in a different manner, by Murray and Cloke (J. Am. Chem. Soc., 56, 2749 (1934)), who reported it to melt at 203-204°. Kohler and Brown stated that the isomeric α,β-diphenylglycidamide melted at 124°.

(51) Darzens, Compt. rend., 142, 214 (1906).

the condensation of ethyl α-chloropropionate and benzaldehyde in the presence of sodium ethylate. Richard[52] reported that this ester could also be obtained from α-chlorophenylacetone, $C_6H_5CH(Cl)COCH_3$, by the following series of reactions:



Discussion of Diphenylacetaldehyde, β,β-Diphenyllactic, β,β-Diphenylacrylic, α,β,β-Triphenyllactic, α,β,β-Triphenylacrylic, and α-Methyl-β,β-diphenyllactic Acids

Diphenylacetaldehyde.

Although several methods for the synthesis of diphenylacetaldehyde are given in the literature, only two of them appear to be of practical value for the preparation of relatively large amounts of the aldehyde. Credit for one of the methods is due to Breuer and Zincke[53], who were the first to describe this compound. They discovered that either hydrobenzoin or isohydrobenzoin* were rearranged to diphenylacetaldehyde when heated in dilute sulfuric acid.

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(52) Richard, Compt. rend., 199, 71 (1934).
(53) Breuer and Zincke, Ann., 198, 141 (182) (1879).

* Hydrobenzoin is the racemic form of 1,2-diphenylethylene glycol; isohydrobenzoin is the meso form of this glycol.

$$C_6H_5CH(OH)CH(OH)C_6H_5 \xrightarrow[\text{heat}]{\text{dil. } H_2SO_4} (C_6H_5)_2CH_2CHO$$

This rearrangement was studied further by Daniloff and Venus-Danilova(54) who, by substituting oxalic acid for sulfuric acid, were able to improve the yield from the procedure.

Behal and Sommelet(55) noted that a reaction occurred when disubstituted ethoxymethyl carbinols were heated with oxalic acid; thus, diphenyl-(ethoxymethyl)-carbinol was converted into diphenylacetaldehyde:

$$(C_2H_5)_2C(OH)CH_2OC_2H_5 \xrightarrow[\text{heat}]{\text{oxalic acid}} (C_6H_5)_2CHCHO$$

By this means they were able to prepare a series of symmetrical, disubstituted acetaldehydes. They obtained the initial carbinol from the reaction of two molecular equivalents of a suitable Grignard reagent with ethyl ethoxyacetate; this procedure was also used by Daniloff and Venus-Danilova(54) with good results.

Burtner and Cusic(56) prepared diphenylacetaldehyde by the oxalic acid rearrangement of dihydrobenzoin (hydrobenzoin) which they obtained by catalytic hydrogenation of benzoin over Raney nickel in dioxane. According to them, the reduction could not be effected with stannous chloride as was reported by Apitsch and Metzger(57).

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(54) Daniloff and Venus-Danilova, Ber., 59, 1032 (1926).
(55) Behal and Sommelet, Bull. soc. chim., (3) 31, 300 (1904).
(56) Burtner and Cusic, J. Am. Chem. Soc. 65, 262 (1943).
(57) Apitsch and Metzger, Ber., 37, 1676 (1904).

β,β-Diphenyllactic Acid.

Weise[58] stated that the hydroxy nitrile, formed from diphenylacetaldehyde and hydrogen cyanide, cannot be hydrolyzed successfully to the corresponding hydroxy acid; the product of the hydrolysis was a tarry substance. In order to prepare the hydroxy acid, Weise turned to the alternate method of converting the nitrile into the imino ether hydrochloride which, upon treatment with water, gave the ester of the desired acid. Hydrolysis of the ester to the acid completed the synthesis.

$$(C_6H_5)_2CHCHO \xrightarrow{HCN} (C_6H_5)_2CHCH(OH)CN \xrightarrow[C_2H_5OH]{HCl} (C_6H_5)_2CHCH(OH)C(=NH)OC_2H_5.HCl$$

$$(C_6H_5)_2CHCH(OH)COOH \xleftarrow[2)\ Hydrolysis]{1)\ H_2O} (C_6H_5)_2CHCH(OH)C(=NH)OC_2H_5.HCl$$

β,β-Diphenylacrylic Acid.

β,β-Diphenylacrylic acid, $(C_6H_5)_2C{=}CHCOOH$, was first prepared by Kohler and Johnstin[59] as part of a study of the reaction between Grignard reagents and unsaturated compounds. They reacted ethyl α-bromocinnamate with phenylmagnesium bromide and obtained β,β-diphenylacrylic acid as one of the products. According to these investigators, the involved reaction proceeded, in part, as follows:

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(58) Weise, Ann., 248, 34 (1888).
(59) Kohler and Johnstin, Am. Chem. J., 33, 35 (1905).

$$C_6H_5CH{=}C(Br)COOC_2H_5 \xrightarrow[2)\ H_2O]{1)\ C_6H_5MgBr} (C_6H_5)_2CHCH(Br)COOC_2H_5$$

$$(C_6H_5)_2CHCH(Br)COOC_2H_5 \xrightarrow[CH_3OH]{KOH} (C_6H_5)_2C{=}CHCOOH$$

In addition to the acrylic acid, benzoic acid and α-bromo-β,β-diphenylpropiophenone, $(C_6H_5)_2CHCH(Br)COC_6H_5$, were also isolated from the reaction mixture. The yield of β,β-diphenylacrylic acid from their procedure was not reported.

Rupe and Busolt[60] desired β,β-diphenylacrylic acid for optical rotation studies, but thought the method of Kohler and Johnstin impractical for its preparation. After several unsuccessful attempts to prepare it by the condensation of benzophenone with malonic acid, using various condensing agents, they proceeded according to the following scheme:

$$(C_6H_5)_2CO \xrightarrow[CH_2BrCOOC_2H_5]{Zn} (C_6H_5)_2C(OH)CH_2COOC_2H_5 \xrightarrow{\text{hydrolysis}}$$

$$(C_6H_5)_2C(OH)CH_2COOH \xrightarrow{\text{dehydration}} (C_6H_5)_2C{=}CHCOOH$$

The first two steps of the synthesis provided good yields of the hydroxy ester and the corresponding acid. Dehydration of the hydroxy acid, by means of freshly distilled acetic anhydride and sodium acetate, gave the acrylic acid apparently without difficulty and in satisfactory yield, although the actual yield was not reported.

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(60) Rupe and Busolt, Ber., 40, 4537 (1907).

This method was employed later by Posner[61] who reported no difficulty but stated that the yield from the dehydration was only 32%.

Rupe and Wolfsleben[62] repeated the synthesis and reported that the dehydration, using acetic anhydride and sodium acetate, failed completely despite several variations in the procedure. These investigators came to the conclusion that Rupe and Busolt must have used crude acetic anhydride, which contained a large amount of acetic acid. Rupe and Wolfsleben then dehydrated the hydroxy ester with formic acid and, without purifying the acrylic ester, proceeded directly to the acrylic acid by hydrolysis. Although no yields were reported, it was stated specifically that the method, which was described in detail, was reliable.

These results were confirmed by Schlenk and Bergmann[63] who isolated the intermediate ethyl β,β-diphenylacrylate by distillation. According to them, the yield of the dehydration always amounted to 50%, based upon the amount of hydroxy ester used.

Burtner and Cusic[56] reported that they prepared β,β-diphenylacrylic acid by known procedures and cited, as references, the work of Rupe and Busolt as well as that of

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(61) Posner, J. prakt. Chem., (2) 82, 425 (1910).
(62) Rupe and Wolfsleben, Ann., 395, 136 (141) (1913).
(63) Schlenk and Bergmann, Ann., 463, 1 (237) (1928).

Natelson and Gottfried[64] who reported on the use of hydrogen chloride as a general method for the dehydration of β-hydroxy esters. Since no details were given by Burtner and Cusic, it is not known which method of dehydration was used by them.

An entirely different procedure for the preparation of β,β-diphenylacrylic acid was reported by Kharasch, Kane and Brown[65]. They prepared it in 50% yield by the interaction of 1, 1-diphenylethylene and oxalyl chloride:

$$(C_6H_5)_2C{=}CH_2 + (COCl)_2 \longrightarrow (C_6H_5)_2C{=}CHCOCl + CO + HCl$$

$$\downarrow H_2O$$

$$(C_6H_5)_2C{=}CHCOOH$$

This method was employed by Bergmann and his associates[66] who, by varying the ratio of the reactants, were able to obtain the desired acid in 95% yield.

α,β,β-Triphenyllactic Acid; α,β,β-Triphenylacrylic Acid.

Kohler and Weiner[67] reported that 1-benzoyl-2,2-diphenylethylene oxide, upon treatment with methanolic potassium hydroxide, was converted into α,β,β-triphenyllactic acid in good yield:

$$(C_6H_5)_2C\underset{\backslash\,/}{-}CHCOC_6H_5 \xrightarrow[CH_3OH]{KOH} (C_6H_5)_2CHC(C_6H_5)(OH)COOH$$

(64) Natelson and Gottfried, J. Am. Chem. Soc., 61, 970 (1939).
(65) Kharasch, Kane and Brown, J. Am. Chem. Soc. 64, 333 (1942).
(66) Bergmann, Weizmann, Dimant, Patai and Szmuskowicz, J. Am. Chem. Soc., 70, 1612 (1948).
(67) Kohler and Weiner, J. Am. Chem. Soc., 56, 434 (1934).

These investigators also prepared the corresponding methyl ester of their acid, by means of the silver salt of the acid, and reported its melting point to be 186°.

Wegmann and Dahn[68] obtained methyl α,β,β-triphenyllactate, m.p. 174-175°, from β-bromophenylpyruvic acid by means of the following series of reactions:

$$C_6H_5CH(Br)COCOOH + C_6H_6 \xrightarrow{AlCl_3} (C_6H_5)_2CHC(C_6H_5)(OH)COOH$$

$$(C_6H_5)_2CHC(C_6H_5)(OH)COOH \xrightarrow{CH_2N_2} (C_6H_5)_2CHC(C_6H_5)(OH)COOCH_3$$

Since their intermediate acid was difficult to purify, they proceeded directly to the ester, and gave no constants for the acid.

Kohler and Weiner found that their lactic acid, when heated above its melting point, was dehydrated to α,β,β-triphenylacrylic acid:

$$(C_6H_5)_2CHC(C_6H_5)(OH)COOH \xrightarrow{heat} (C_6H_5)_2C{=}C(C_6H_5)COOH + H_2O$$

<u>α-Methyl-β,β-diphenyllactic Acid</u>.

As far as we are aware, α-methyl-β,β-diphenyllactic acid has not been described in the literature. Methyl α-methyl-β,β-diphenyllactate was described by Kohler and Weiner[67] who reported that it was formed in 85% yield by the interaction of methyl diphenylpyruvate and methylmagnesium iodide. These investigators reported the melting point of their ester

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(68) Wegmann and Dahn, Helv. Chim. Acta, <u>29</u>, 415 (1946).

to be 87-88°, but did not hydrolyze it to the corresponding acid.

$$(C_6H_5)_2CHCOCOOCH_3 \xrightarrow{CH_3MgI} (C_6H_5)_2CHC(CH_3)(OH)COOCH_3$$

As has been stated previously, Bardon and Ramart[44] claimed that the action of methylmagnesium iodide on ethyl β,β-diphenylglycidate yielded an ester, m.p. 73°, the corresponding acid of which melted at 167°. Their acid was stated to be β-methyl-β,β-diphenyllactic acid.

$$(C_6H_5)_2C(O)CHCOOC_2H_5 \xrightarrow{CH_3MgI} (C_6H_5)_2C(CH_3)CH(OH)COOC_2H_5$$

$$(C_6H_5)_2C(CH_3)CH(OH)COOC_2H_5 \xrightarrow{\text{hydrolysis}} (C_6H_5)_2C(CH_3)CH(OH)COOH$$

Kohler, Richtmyer and Hester[41] expressed the opinion that the initial ester of Bardon and Ramart was actually the isomeric ketonic ester in which case the product of the Grignard reaction would be expected to be α-methyl-β,β-diphenyllactic acid[67].

$$(C_6H_5)_2CHCOCOOC_2H_5 \xrightarrow{CH_3MgI} (C_6H_5)_2CHC(CH_3)(OH)COOC_2H_5$$

$$(C_6H_5)_2CHC(CH_3)(OH)COOC_2H_5 \xrightarrow{\text{hydrolysis}} (C_6H_5)_2CHC(CH_3)(OH)COOH$$

DISCUSSION OF THIS INVESTIGATION

During this investigation we prepared β-diethylaminoethyl esters of the following acids:

Acetic Acids.

$C_6H_5CH(Cl)COOH$

$C_6H_5CH(Br)COOH$

$C_6H_5CH(NMe_2)COOH$

$C_6H_5CH(NC_5H_{10})COOH$

$C_6H_5CH(NC_4H_8O)COOH$

$(C_6H_5)_2C(Cl)COOH$

$(C_6H_5)_2C(Br)COOH$

$(C_6H_5)_2C(OC_2H_5)COOH$

$(C_6H_5)_2C(NMe_2)COOH$

Propionic Acids.

$(C_6H_5)_2CHCH(OH)COOH$

$(C_6H_5)_2CHC(OH)(C_6H_5)COOH$

$(C_6H_5)_2CHC(OH)(CH_3)COOH$

$(C_6H_5)_2C(OH)CH(OH)COOH$

$(C_6H_5)_2C\text{-}CHCOOH$ (O)

$C_6H_5CH\text{-}C(CH_3)COOH$ (O)

$C_6H_5CH\text{-}C(C_6H_5)COOH$ (O)

Acrylic Acids.

$(C_6H_5)_2C{=}C(C_6H_5)COOH$

$(C_6H_5)_2C{=}C(Br)COOH$

Although we were interested especially in esters of glycidic acids, esters of other substituted propionic, acrylic and acetic acids were prepared for pharmacological study.

Acetic Acids.

As far as we have been able to ascertain, basic-alkyl esters of acetic acid, in which a nitrogen-containing group is present in the α-position of the acetic acid, have not been extensively studied. β-Diethylaminoethyl 1-methyl-4-(α-thienyl)-piperidine-4-carboxylate dihydrochloride has been prepared and tested for analgesic activity(69). Another reference to this type of compound is in the patent literature(70) where β-diethylaminoethyl α-(α-pyridyl)-phenylacetate and β-diethylaminoethyl α-(α-piperidyl)-phenylacetate are stated to have physiological properties.

We therefore felt that the preparation and pharmacological evaluation of a few more esters of this type would be of interest. Accordingly, we prepared β-diethylaminoethyl esters of the following acids: α-dimethylaminophenylacetic, α-morpholinophenylacetic, α-piperidinophenylacetic, and α-dimethylaminodiphenylacetic acids.

These esters were prepared by the amination of the basic esters of the corresponding α-bromo acetic acids as is indicated by the following example:

$$C_6H_5CH(Br)COOCH_2CH_2N(C_2H_5)_2 \xrightarrow{(CH_3)_2NH} C_6H_5\underset{\displaystyle N(CH_3)_2}{\underset{|}{C}}HCOOCH_2CH_2N(C_2H_5)_2$$

Certain of the intermediate halogen esters were cyclized to

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(69) Chanin, Dissertation, University of Michigan, (1946).
(70) British Patent, 589,625; Chem. Abst., 42, 225 (1948).

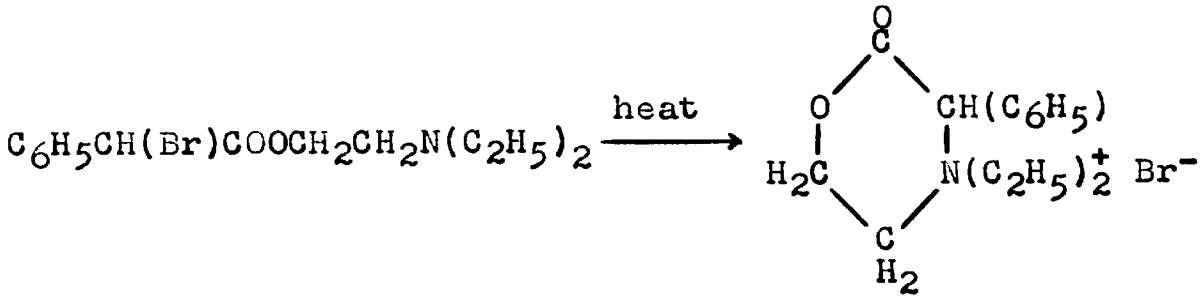
morpholone derivatives which were also of interest as possible antispasmodic agents.

β-Diethylaminoethyl α-bromophenylacetate was obtained from the interaction of β-diethylaminoethanol and α-bromophenacetyl bromide. Although it was found possible to prepare the latter substance from phenylacetic acid by means of phosphorous and bromine[71], a better yield was obtained from the interaction of mandelic acid and phosphorous pentabromide*, a procedure used by Cohen[72].

$$C_6H_5CH(OH)COOH \xrightarrow{PBr_5} C_6H_5CH(Br)COBr \xrightarrow{HOCH_2CH_2N(C_2H_5)_2} C_6H_5CH(Br)COOCH_2CH_2N(C_2H_5)_2$$

The bromo ester was reacted, separately, with dimethylamine, piperidine and morpholine to form the corresponding α-dimethylamino, α-piperidino, and α-morpholino esters, all of which were obtained in good yield.

β-Diethylaminoethyl α-bromophenylacetate was also cyclized, by heat, to form 3-phenyl-4-ethylmorpholone-2 ethobromide.



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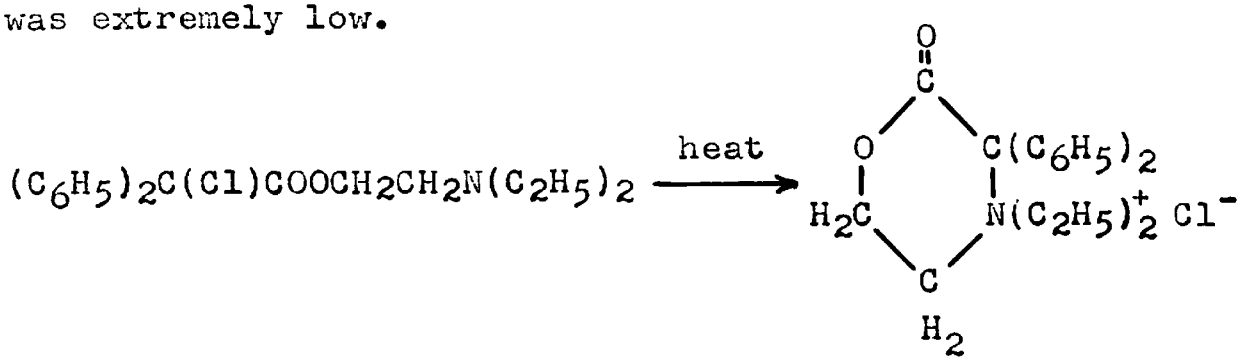
(71) Anshütz, Hahn and Walter, Ann., 354, 117 (127) (1907).

* This material was prepared by the procedure described by Carothers (J. Am. Chem. Soc., 48, 3192 (1926).

(72) Cohen, J. Chem. Soc., 99, 1058 (1911).

When an attempt was made to cyclize the corresponding α-chloro ester*, the only product obtained was a resinous gum.

It was found that, while the basic ester of α-chlorophenylacetic acid cyclized less readily than the corresponding α-bromo ester, the basic ester of α-chlorodiphenylacetic acid cyclized more readily than the corresponding α-bromo ester. The yield of the morpholone in the latter instance was extremely low.



In order to obtain the basic ester of α-chlorodiphenylacetic acid, benzilic acid was converted into α-chlorodiphenacetyl chloride by means of phosphorous pentachloride in the manner described by Bickel(73). The acid chloride was then reacted with β-diethylaminoethanol to form β-diethylaminoethyl α-chlorodiphenylacetate hydrochloride(56).

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* This compound was prepared from the reaction between β-diethylaminoethanol and α-chlorophenacetyl chloride. The latter substance was obtained from mandelic acid and phosphorous pentachloride as described by Staudinger (Ber., 44, 533 (1911).

(73) Bickel, Ber., 22, 1537 (1889).

We found that β-diethylaminoethyl α-bromodiphenylacetate was conveniently prepared from the corresponding benzilic ester by means of anhydrous hydrogen bromide. The benzilic ester was obtained from benzilic acid by means of the Horenstein-Pählicke esterification[74].

$$(C_6H_5)_2C(OH)COOCH_2CH_2N(C_2H_5)_2 \xrightarrow{HBr} (C_6H_5)_2C(Br)COOCH_2CH_2N(C_2H_5)_2 \cdot HBr$$

Irrespective of whether the benzilic ester base or the hydrochloride was employed as the starting material, the product isolated directly from the reaction mixture was the bromo ester hydrobromide.

The bromo ester reacted very readily with ethanol to form the hitherto undescribed β-diethylaminoethyl α-ethoxydiphenylacetate. Treatment of the bromo ester with dimethylamine converted it into β-diethylaminoethyl α-dimethylaminodiphenylacetate.

$$(C_6H_5)_2C(Br)COOCH_2CH_2N(C_2H_5)_2 \xrightarrow{C_2H_5OH} (C_6H_5)_2C(OC_2H_5)COOCH_2CH_2N(C_2H_5)_2$$

$$(C_6H_5)_2C(Br)COOCH_2CH_2N(C_2H_5)_2 \xrightarrow{(CH_3)_2NH} (C_6H_5)_2C(N(CH_3)_2)COOCH_2CH_2N(C_2H_5)_2$$

Propionic Acids.

β,β-Diphenylglycidic Acid.

We investigated the condensation of benzophenone and ethyl chloroacetate in order to clarify, if possible, the

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(74) Horenstein and Pählicke, Ber., 71, 1644 (1938).

disagreement in the literature concerning the product from this reaction. It was also desired to obtain ethyl β,β-diphenylglycidate by this means, and to use this ester as an intermediate in the preparation of the corresponding acid which was to be esterified with a basic alcohol. The resulting basic ester was considered to be of interest as a possible antispasmodic agent. A search of the literature revealed no case in which a basic ester of a glycidic acid has ever been prepared and tested for pharmacological activity.

We found that the product from the condensation of benzophenone and ethyl chloroacetate, using either sodamide or sodium ethylate as the condensing agent, was ethyl β,β-diphenylglycidate.

$$(C_6H_5)_2CO + ClCH_2COOC_2H_5 \xrightarrow[NaOC_2H_5]{NaNH_2 \text{ or}} (C_6H_5)_2C\underset{\backslash\,/}{-}CHCOOC_2H_5 \quad (O)$$

Some investigators preferred sodamide as the condensing agent in a procedure which was conducted at room temperature or below, claiming that the best yields were obtained in this manner. Others, however, reported better yields and less side reactions when sodium ethylate was employed. In the latter procedure, a higher temperature was maintained in the last stages of the condensation. Both methods were used in our work and it was found that the sodium ethylate method gave higher yields, perhaps because of the elevated temperature. Alcohol-free sodium ethylate was always employed;

it has been reported recently(43) that optimum yields of a glycidic ester were realized in a similar condensation by the use of this agent. The same authors also reported that the yield was lowered by the use of sodamide in place of a sodium alcoholate.

Our condensation procedure differed slightly from those of Darzens(34), and of Kohler and co-workers(41) who conducted the condensation in the absence of a solvent. We felt that a better dispersion, hence a more effective action, of the condensing agent was attained when the mixture was diluted with an equal volume of anhydrous ether. The solvent was removed prior to the heating period necessary to complete the reaction. The reaction mixture was subsequently treated in the manner described by the above-mentioned investigators with the exception that the crude product was carefully neutralized before distillation, and the distillation was carried out at a lower temperature. Distillation of the crude material yielded a mixture which consisted mainly of the glycidic ester but also contained an appreciable quantity of the isomeric pyruvic ester. These esters cannot be readily separated by fractional distillation, since their boiling points are nearly identical, but can be separated by recrystallization from ethanol in which the glycidic ester is less soluble. The pyruvic ester remained in the mother liquor from which it was isolated by fractional distillation.

The pure glycidic ester, contrary to the reports of earlier investigators, can be distilled unchanged at

temperatures as high as 190-193° (11 mm.). The ester reacted with ammonia to form an amide which melted at 148-149°. The amide obtained from ethyl diphenylpyruvate melted at 167-168°.

The acid obtained from our glycidic ester by Claisen's method was fairly unstable at ordinary temperature. When heated above its melting point, gas was evolved and the residual oil was shown to be diphenylacetaldehyde by its boiling point, and by its semicarbazone, a well-known derivative.

When the glycidic ester was heated for a short time at 200° in the presence of small amounts of either hydrogen chloride or glacial acetic acid, it was converted, quantitatively, into the isomeric ethyl diphenylpyruvate.

$$(C_6H_5)_2C(O)CHCOOC_2H_5 \xrightarrow[\text{heat}]{H^+} (C_6H_5)_2CHCOCOOC_2H_5$$

No such rearrangement was noted in the absence of an acid. The same type of rearrangement was observed in the case of the corresponding methyl glycidic ester, which was converted into the isomeric pyruvic ester under the same conditions. Similarly, β,β-diphenylglycidamide was rearranged to diphenylpyruvamide.

Ethyl diphenylpyruvate is a yellow oil, b.p. 152-155° (1 mm.) which, when inoculated with seed crystals that had been obtained by the method described by Kohler and his associates[41], solidified and melted at 37°; its phenylhydrazone melted at 101-102°. These properties agree with those

reported by Kohler et al. for these compounds. Hydrolysis of the ester by Claisen's method yielded the sodium salt of the corresponding acid from which the free acid was liberated by the acidification of an aqueous solution. After recrystallization from water, the acid melted at 85-87°, and was shown to be the monohydrate of diphenylpyruvic acid; the monohydrate has not been described previously. It was readily dehydrated by means of boiling chloroform, and the anhydrous acid melted at 116-117°. The process is reversible in that recrystallization from water hydrates the anhydrous acid. The properties of our diphenylpyruvic acid were in complete agreement with those reported in the literature for this compound.

It was interesting to find that the purest sample of our glycidic ester, as well as the pyruvic ester, gave a green color when treated with ferric chloride in alcohol, although the color developed more slowly in the case of the glycidic ester*. We found that β,β-diphenylglycidamide and the corresponding pyruvamide also gave a positive test with ferric chloride; again, the color development was more rapid with the keto compound. Furthermore, our glycidic ester liberated iodine from a solution of potassium iodide in acetic acid.

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* Milas and his associates(43) reported similar results with their glycidic ester, and attributed their result to the presence of the enol form of the corresponding keto ester.

Benzophenone was also condensed with methyl chloroacetate, by means of sodamide, to yield a new compound, methyl β,β-diphenylglycidate. The glycidic ester was easily converted, by heat in the presence of an acid, into the isomeric methyl diphenylpyruvate, which had been described by Kohler, Richtmyer and Hester[41]. Methyl diphenylpyruvate was also obtained by the direct esterification of diphenylpyruvic acid using a mineral acid catalyst*. It was also found possible to prepare small amounts of diphenylpyruvyl chloride which, when treated with methanol, yielded methyl diphenylpyruvate.

Kohler and his associates[41] obtained ethyl β,β-diphenylglycerate by steam distillation of their crude glycidic ester condensation product. We failed to observe similar results with our crude ester until it had been made distinctly acidic. Evidently, the presence of an acid is necessary for this reaction to take place at an appreciable rate. Our pure glycidic ester was converted almost quantitatively into the glyceric ester when it was refluxed in water to which a small amount of hydrochloric acid had been added.

Considerable difficulty was encountered in the hydrolysis of ethyl β,β-diphenylglycerate. In all of the hydrolytic

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* It has been reported (Simon, Ber., 26, 769 (1893)) that certain pyruvic acids may be esterified in the absence of a mineral acid catalyst. We found that diphenylpyruvic acid can be converted into its methyl ester by refluxing a methanolic solution of the acid, but the yield of the ester from this process is low.

procedures used, an appreciable amount of an unidentified, non-acidic material was invariably formed, and the yield of the glyceric acid was consequently low. The best procedure found, consisting of a brief reaction period using aqueous sodium carbonate, gave only a 45% yield of the desired acid. The amide of the glyceric acid was prepared by the amidification of the ester, and served as a check on the identity of these glyceric acid derivatives.

An attempt was made to prepare β-diethylaminoethyl diphenylpyruvate by the Horenstein-Pählicke procedure[74] which has been used so extensively for the preparation of a wide variety of basic-alkyl esters.

$$(C_6H_5)_2CHCOCOOH + ClCH_2CH_2N(C_2H_5)_2 \xrightarrow[\text{alcohol}]{\text{isopropyl}} (C_6H_5)_2CHCOCOOCH_2CH_2N(C_2H_5)_2 \cdot HCl$$

Diphenylpyruvic acid and β-diethylaminoethyl chloride were allowed to react in boiling isopropyl alcohol after which the solvent was removed, and the oily residue was triturated under anhydrous ether. The crystalline solid, so obtained, was water-soluble and it was expected that it was the basic ester hydrochloride of the pyruvic acid. However, when the product was analyzed, its analytical data conformed to that of β-diethylaminoethanol hydrochloride. A mixed melting point with an authentic sample of β-diethylaminoethanol hydrochloride established the identity of the compound. The yield of this material from the reaction indicated that

nearly all of the initial β-diethylaminoethyl chloride had been converted into the corresponding alcohol hydrochloride.

We suspected that, in the reaction described above, the acid had been converted into the unknown isopropyl ester. Since the ethyl ester was a known substance, the experiment was repeated using ethanol instead of isopropyl alcohol as the solvent. In this instance we again obtained the alcohol hydrochloride in 87% yield (based on the initial amount of the basic-alkyl chloride used) and ethyl diphenylpyruvate in an amount which accounted for nearly 100% of the initial diphenylpyruvic acid.

The reaction evidently proceeded in the following manner:

$$(C_6H_5)_2CHCOCOOH + ClCH_2CH_2N(C_2H_5)_2 + C_2H_5OH \longrightarrow$$

$$(C_6H_5)_2CHCOCOOC_2H_5 + HOCH_2CH_2N(C_2H_5)_2 \cdot HCl$$

Attempts, made to effect this esterification in non-alcoholic solvents such as chloroform, dioxane and acetone, in an effort to avoid the formation of the simple ester, were likewise unsuccessful. Only small amounts of crystalline material were isolated in each case and these products were extremely difficult to purify. Moreover, the use of the different solvents gave rise to different products, none of which were positively identified. The acid did not react with the hydrochloride of the basic alcohol. Although it was found possible to prepare very small amounts of diphenylpyruvyl chloride by means of thionyl chloride, when slightly larger

amounts were prepared and reacted with the basic alcohol, only a water-insoluble oil was obtained. Despite the many attempts using these various procedures, we were unable to prepare a basic-alkyl ester hydrochloride of diphenylpyruvic acid.

Since Kohler and his associates[41] were unable to isolate ethyl β,β-diphenylglycidate in the pure state, they used their crude condensation product, which was a mixture of the ester, benzophenone and ethyl chloroacetate, in their study of the reaction between phenylmagnesium bromide and ethyl β,β-diphenylglycidate. It was of interest, therefore, to determine the nature of the products formed by this reaction when pure ethyl β,β-diphenylglycidate was employed.

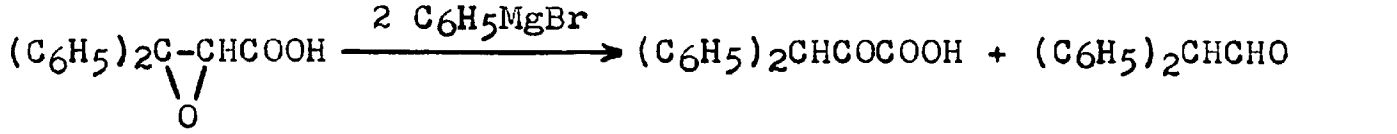
Pure ethyl β,β-diphenylglycidate was treated at 20° with five molecular equivalents of phenylmagnesium bromide. The product was found to be a mixture from which biphenyl, diphenylacetaldehyde and triphenylcarbinol were isolated and definitely identified.

$$(C_6H_5)_2C\underset{O}{\diagdown\!\diagup}CHCOOC_2H_5 \xrightarrow{5\ C_6H_5MgBr} (C_6H_5)_2 + (C_6H_5)_2CHCHO + (C_6H_5)_3COH$$

These results are in accord with those reported by Kohler and his co-workers.

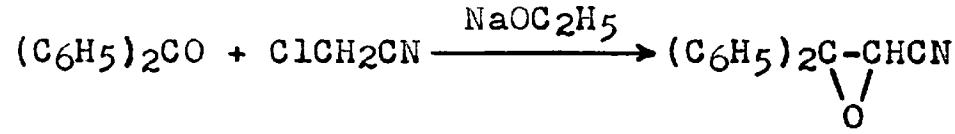
It was also considered of interest to study the reaction between β,β-diphenylglycidic acid and phenylmagnesium bromide in order to determine if the acid, as well as the ester, was cleaved by the Grignard reagent. When two moles of phenylmagnesium bromide were reacted with one mole of β,β-diphenylglycidic acid at 10-15°, diphenylpyruvic acid and diphenylacetaldehyde were formed. We cannot suggest any reaction mechanism

which adequately explains the formation of these products.

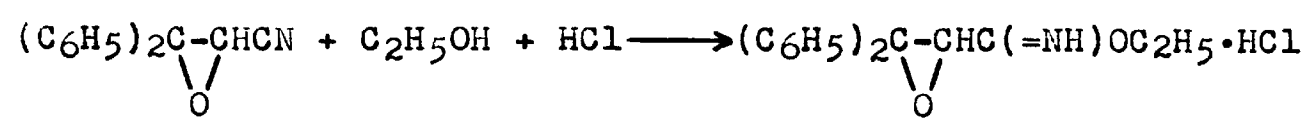


β,β-Diphenylglycidonitrile.

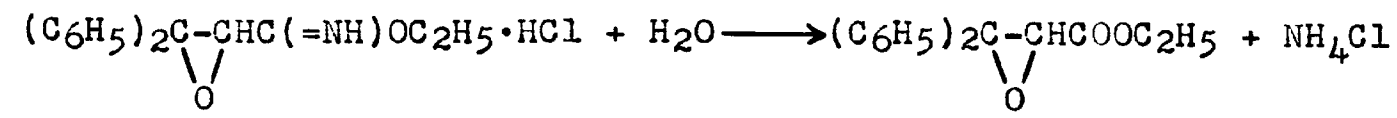
As far as we are aware, α-chloronitriles have never been used as the halogen component in the Darzens glycidic ester condensation. We found that α-chloroacetonitrile condensed with benzophenone, in the presence of sodium ethylate, to form a substance which we believe was β,β-diphenylglycidonitrile.



The epoxy nitrile reacted with the calculated amounts of ethanol and hydrogen chloride, in anhydrous ether, to form the corresponding imino ether hydrochloride (ethyl β,β-diphenylglycidimino ethyl ether hydrochloride).



When the imino ether hydrochloride was dissolved in water, an ester, whose properties agreed with those of ethyl β,β-diphenylglycidate, was obtained.



It was expected that heat would convert the imino ether hydrochloride into β,β-diphenylglycidamide and ethyl chloride. However, when the compound was heated above its melting point, a gas was evolved, and the residue was found to be diphenylpyruvamide.

$$(C_6H_5)_2C\underset{O}{\diagdown\diagup}CHC(=NH)OC_2H_5 \cdot HCl \xrightarrow{\text{heat}} (C_6H_5)_2CHCOCONH_2 + C_2H_5Cl$$

Although we are uncertain about the mechanism by which the pyruvamide was formed, it was shown, in a separate experiment, that when the glycidamide was heated in the presence of a trace of hydrogen chloride, it rearranged with the formation of the pyruvamide.

In order to establish the structure of β-diethylaminoethyl β,β-diphenylglycidate, obtained from the interaction of β,β-diphenylglycidic acid and β-diethylaminoethyl chloride in boiling isopropyl alcohol (Horenstein-Pählicke procedure), it was considered advisable to prepare the basic ester by another method. The second synthetic method employed consisted of the condensation of β-diethylaminoethyl α-chloroacetate with benzophenone by the use of sodamide. The required chloro ester was obtained, as its hydrochloride, from the reaction between chloroacetyl chloride and β-diethylaminoethanol. As far as we are aware, the use of a basic ester of a chloroacetic acid in the Darzens glycidic ester condensation has never been described in the literature.

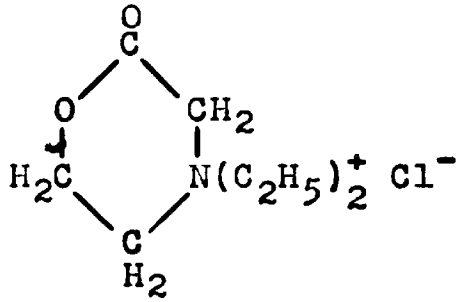
$$ClCH_2COCl + HOCH_2CH_2N(C_2H_5)_2 \longrightarrow ClCH_2COOCH_2CH_2N(C_2H_5)_2 \cdot HCl$$

$$(C_6H_5)_2CO + ClCH_2COOCH_2CH_2N(C_2H_5)_2 \xrightarrow{NaNH_2} (C_6H_5)_2C\text{-}CHCOOCH_2CH_2N(C_2H_5)_2$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad \backslash\,/$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad O$$

The condensation product was isolated as its hydrochloride salt and, although formed in poor yield, was found to be identical with the basic ester obtained from the direct esterification of β,β-diphenylglycidic acid.

The chloro ester has not been reported in the literature. Its hydrochloride salt, as obtained from the reaction mixture, was a hygroscopic solid for which no suitable means of purification could be found. After the base had been liberated from the salt, it was distilled. The oily distillate gradually became crystalline and, after several days, nearly completely solidified. This product was very soluble in water, and contained ionizable chlorine. In view of this latter property, we believe that the ester base underwent cyclization with the formation of a morpholone.

$$ClCH_2COOCH_2CH_2N(C_2H_5)_2 \xrightarrow{\text{heat}}$$

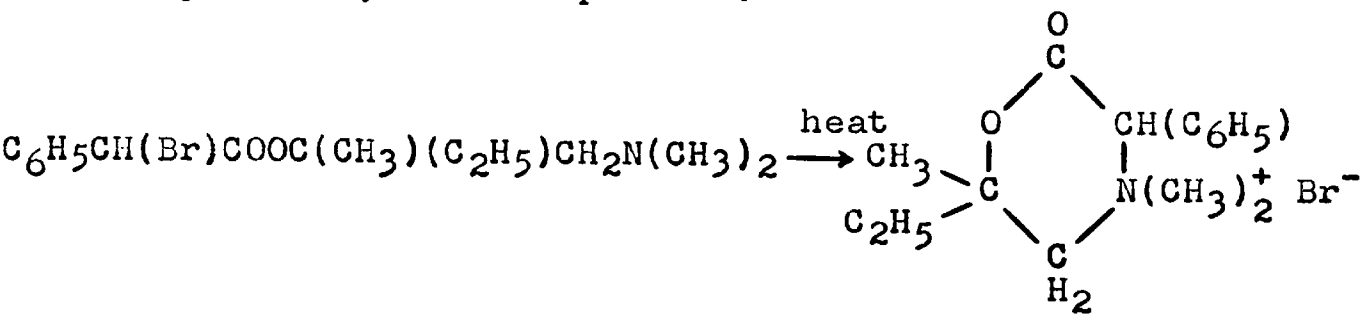


The assumption that the ester base cyclized to a morpholone received support from the experiments described by Fourneau[75]. This investigator showed definitely that the β-dimethylamino-α-methyl-α-ethylethanol ester of

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(75) Fourneau, Bull. soc. chim., (4) 3, 1141 (1908).

α-bromophenylacetic acid cyclizes spontaneously, at steam-bath temperature, to a morpholone.



Our morpholone was submitted for pharmacological evaluation, since its sturcture suggested that it might have antispasmodic activity. Other compounds of a similar structure were also prepared, and are discussed later.

α,β-Diphenylglycidic Acid.

The Darzens glycidic ester condensation was employed by us for the preparation of ethyl α,β-diphenylglycidate from which α,β-diphenylglycidic acid was obtained by hydrolysis. Ethyl mandelate, prepared by the esterification of mandelic acid in the usual manner, was converted into ethyl α-chlorophenylacetate by the excellent method described by Darzens[76] in which thionyl chloride and pyridine are used. The chloro ester was then condensed with benzaldehyde in the presence of sodium ethylate in order to obtain ethyl α,β-diphenylglycidate. Hydrolysis of the ester by Claisen's method yielded the desired α,β-diphenylglycidic acid, m.p. 121-122° (dec.).

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(76) Darzens, Compt. rend., 152, 1601 (1911).

$$C_6H_5CH(OH)COOH \xrightarrow[HCl]{C_2H_5OH} C_6H_5CH(OH)COOC_2H_5$$

$$C_6H_5CH(OH)COOC_2H_5 \xrightarrow[pyridine]{SOCl_2} C_6H_5CH(Cl)COOC_2H_5$$

$$C_6H_5CH(Cl)COOC_2H_5 + C_6H_5CHO \xrightarrow{C_2H_5ONa} C_6H_5CH\text{-}C(C_6H_5)COOC_2H_5 \quad (\text{O bridge})$$

$$C_6H_5CH\text{-}C(C_6H_5)COOC_2H_5 \xrightarrow{\text{hydrolysis}} C_6H_5CH\text{-}C(C_6H_5)COOH \quad (\text{O bridge})$$

The melting point of our acid corresponded to the melting point (121°) reported by Kohler and Brown[50] for one of the forms of α,β-diphenylglycidic acid obtained by them (see discussion page 38).

Treatment of our ethyl α,β-diphenylglycidate with ammonia in dilute ethanol yielded α,β-diphenylglyceramide, m.p. 133-134°.

$$C_6H_5CH\text{-}C(C_6H_5)COOC_2H_5 + NH_3 + H_2O \xrightarrow{C_2H_5OH} C_6H_5CH(OH)C(C_6H_5)(OH)CONH_2 \quad (\text{O bridge})$$

When our acid was esterified by the use of diazomethane, we obtained a methyl ester which melted at 71-72°; after it had melted and resolidified, the ester melted at 79-80°. Kohler and Brown also reported that a methyl ester obtained by them melted at 80°.

As stated above, the melting points of our methyl α,β-diphenylglycidate, α,β-diphenylglycidic acid and α,β-diphenylglyceramide corresponded to those reported by Kohler and Brown.

However, these investigators also described a second form of each of these compounds which we never detected in any of our reaction mixtures.

α-Methyl-β-phenylglycidic Acid.

We prepared α-methyl-β-phenylglycidic acid by means of the same general reactions used for the preparation of α,β-diphenylglycidic acid. Ethyl α-chloropropionate, made from ethyl lactate according to the method of Darzens[76], was condensed with benzaldehyde by means of sodamide. The relatively low yield of pure ethyl α-methyl-β-phenylglycidate was believed to be due to the condensing agent employed. α-Methyl-β-phenylglycidic acid was obtained from the ester by means of Claisen's method of hydrolysis.

$$CH_3CH(OH)COOC_2H_5 \xrightarrow[\text{pyridine}]{SOCl_2} CH_3CH(Cl)COOC_2H_5$$

$$CH_3CH(Cl)COOC_2H_5 + C_6H_5CHO \xrightarrow{NaNH_2} C_6H_5CH\text{-}C(CH_3)COOC_2H_5 \quad (\text{O bridge})$$

$$C_6H_5CH\text{-}C(CH_3)COOC_2H_5 \xrightarrow{\text{hydrolysis}} C_6H_5CH\text{-}C(CH_3)COOH \quad (\text{O bridge})$$

As an additional check on the identity of our acid, it was heated for one hour at 150-160° in order to convert it into carbon dioxide and phenylacetone:

$$C_6H_5CH\text{-}C(CH_3)COOH \xrightarrow{\text{heat}} C_6H_5CH_2COCH_3 + CO_2 \quad (\text{O bridge})$$

The residual phenylacetone was identified by means of its semicarbazone.

Diphenylacetaldehyde.

In our work, diphenylacetaldehyde was prepared by two different methods. The first was that of Behal and Sommelet[55], which had been repeated and described in detail by Daniloff and Venus-Danilova[54]. Ethyl chloroacetate was converted into ethyl ethoxyacetate by means of sodium ethylate in boiling ethanol. Interaction of the ethoxy compound with two molecular equivalents of phenylmagnesium bromide yielded diphenyl-(ethoxymethyl)-carbinol. Treatment of the carbinol with oxalic acid at 120° for three hours converted it into diphenylacetaldehyde, which was purified by distillation, and identified by means of its semicarbazone.

$$ClCH_2COOC_2H_5 \xrightarrow{C_2H_5ONa} C_2H_5OCH_2COOC_2H_5 \xrightarrow{2\ C_6H_5MgBr} C_2H_5OCH_2C(C_6H_5)_2OH$$

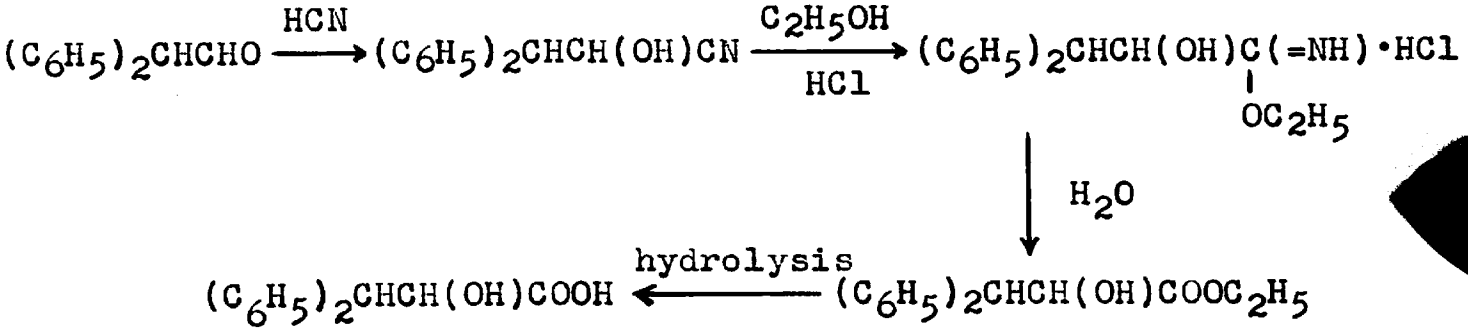
$$C_2H_5OCH_2C(C_6H_5)_2OH \xrightarrow{\text{oxalic acid}} (C_6H_5)_2CHCHO$$

Diphenylacetaldehyde was also obtained from β,β-diphenylglycidic acid by the Darzens aldehyde synthesis, which, as far as is known, has never been employed successfully in the preparation of this material. It is true that Troell[39] claimed to have obtained, by this procedure, a small amount of material, which he qualitatively identified as an aldehyde. However, he did not actually obtain the aldehyde in the pure state. Pointet[38], who presumably had the glycidic ester,

was unable to rearrange the acid derived from it to diphenylacetaldehyde, presumably because his acid was actually the isomeric ketonic acid. We found that diphenylacetaldehyde may be obtained in good yield by this method. The pure glycidic ester was prepared in 48% yield and was hydrolyzed in 70% yield to the corresponding acid, the pyrolysis of which gave the desired aldehyde; the yield of distilled aldehyde from the pyrolysis was 76%.

β,β-Diphenyllactic Acid.

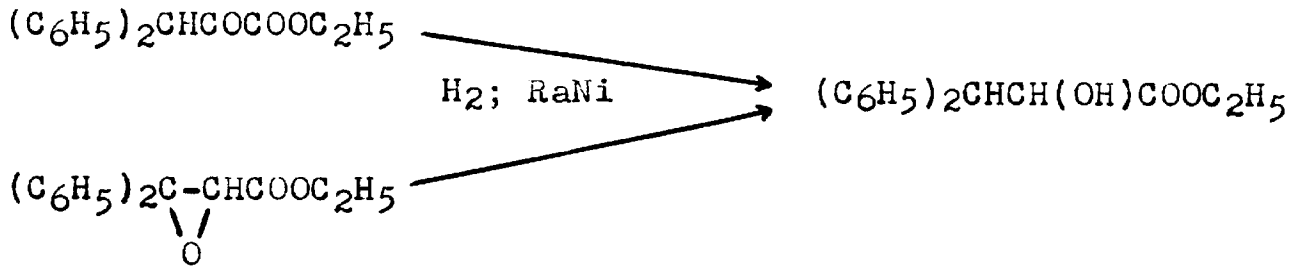
In our early work, we prepared β,β-diphenyllactic acid by following the directions given by Weise[58] for the preparation of this acid. Diphenylacetaldehyde was reacted with hydrogen cyanide, and the resulting α-hydroxy-β,β-diphenylpropionitrile was converted into its imino ether hydrochloride by means of ethanol and hydrogen chloride. The imino ether hydrochloride was then treated with water, whereupon it was converted into ethyl β,β-diphenyllactate; the ester was then hydrolyzed to the desired acid.



The over-all yield of β,β-diphenyllactic acid from the synthesis was low because of the poor yield of the intermediate

imino ether salt; in two attempts, this yield did not exceed 27%. Conversion of the imino ether salt into the ester, and the hydrolysis of the ester took place nearly quantitatively.

We found much better methods for the preparation of β,β-diphenyllactic acid. Catalytic reduction of ethyl diphenylpyruvate over Raney nickel in ethanol gave a quantitative yield of the lactic ester, which was subsequently hydrolyzed to the acid. It was also found that catalytic reduction of ethyl β,β-diphenylglycidate, under the same conditions, produced ethyl β,β-diphenyllactate in excellent yield.



As far as is known, no example of the catalytic reduction of a glycidic ester has been reported in the literature.

We also found that the reduction of ethyl β,β-diphenylglycidate with sodium and alcohol gave a small yield (27%) of β,β-diphenyllactic acid and an unidentified oil. These results were in accord with those reported by Billon-Bardon[47], but did not agree with those of Verley[49]. In view of the work of the latter investigator, the products of our reduction would be expected to be β,β-diphenylpropionic acid and 3,3-diphenyl-propanol-1.

$$(C_6H_5)_2C(O)CHCOOC_2H_5 \xrightarrow[C_2H_5OH]{Na} (C_6H_5)_2CHCH_2COOH + (C_6H_5)_2CHCH_2CH_2OH$$

Diphenylpyruvic acid was reduced smoothly to β,β-diphenyllactic acid by means of hydrogen in the presence of a palladium-charcoal catalyst in alcohol solution.

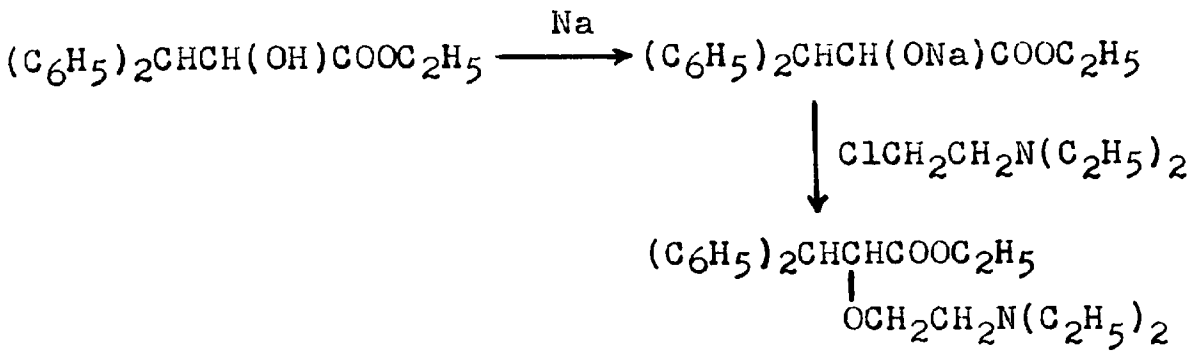
$$(C_6H_5)_2CHCOCOOH \xrightarrow[Pd\text{-}C]{H_2} (C_6H_5)_2CHCH(OH)COOH$$

Ethyl α-(β-Diethylaminoethoxy)-β,β-diphenylpropionate.

It was considered of interest to prepare a representative basic ether of ethyl β,β-diphenyllactate, and to have such a compound examined for antispasmodic activity. The etherification of the lactic ester was accomplished by following the directions stated by Hoffman and von Meyenburg(77) for the preparation of the basic ether of ethyl benzilate. The sodium derivative of ethyl β,β-diphenyllactate, obtained from the ester and powdered sodium, was reacted with β-diethylaminoethyl chloride to form ethyl α-(β-diethylaminoethoxy)-β,β-diphenylpropionate. Its hydrochloride salt was prepared from the base and ethereal hydrogen chloride.

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(77) Hoffman and von Meyenburg, U.S. Patent, 2,387,447; Chem. Abst., 40, 1175 (1946).



α,β,β-Triphenyllactic Acid; α,β,β-Triphenylacrylic Acid.

We prepared α,β,β-triphenyllactic acid by means of the reaction between diphenylpyruvic acid and two molecular equivalents of phenylmagnesium bromide in ether solution.

$$(C_6H_5)_2CHCOCOOH \xrightarrow{2\ C_6H_5MgBr} (C_6H_5)_2CHC(OH)(C_6H_5)COOH$$

The reaction proceeded smoothly and provided the desired acid, the properties of which agreed with those reported for it by Kohler and Weiner[67]. Its methyl ester, obtained by direct esterification of the acid, melted at 183-184°*.

When α,β,β-triphenyllactic acid was heated at a temperature above its melting point, it decomposed with brisk evolution of water to form α,β,β-triphenylacrylic acid.

$$(C_6H_5)_2CHC(OH)(C_6H_5)COOH \xrightarrow{heat} (C_6H_5)_2C{=}C(C_6H_5)COOH + H_2O$$

Both the process and the acrylic acid have been described in the literature[67].

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* Kohler and Weiner[67] reported 186°, while Wegmann and Dahn[68] found 174-175°.

α-Methyl-β,β-diphenyllactic Acid.

When diphenylpyruvic acid was treated with two molecular equivalents of methylmagnesium iodide in ether solution, we obtained an acid, m.p. 167-168.5°, which was α-methyl-β,β-diphenyllactic acid.

$$(C_6H_5)_2CHCOCOOH \xrightarrow{2\ CH_3MgI} (C_6H_5)_2CHC(OH)(CH_3)COOH$$

The methyl and ethyl esters of our acid, prepared by the direct esterification of the acid, melted at 88-89° and 73-74°, respectively.

As has been stated, Bardon and Ramart[44] isolated an ester, m.p. 73°, from the reaction between methylmagnesium iodide and a compound which they believed was ethyl β,β-diphenylglycidate. The acid, which they obtained by hydrolysis of their ester, melted at 167°, and was claimed to be β-methyl-β,β-diphenyllactic acid. However, Kohler and his co-workers[41] later expressed the opinion that the initial ester used by Bardon and Ramart was ethyl diphenylpyruvate instead of the glycidic ester; in this case, the ester (m.p. 73°) formed in the Grignard reaction would be ethyl α-methyl-β,β-diphenyllactate, and the acid, m.p. 167°, would be the α-methyl- rather than the β-methyllactic acid.

In a later publication, Kohler and Weiner[67] reported that methyl α-methyl-β,β-diphenyllactate, m.p. 87-88°, was formed from the interaction of methylmagnesium iodide and methyl diphenylpyruvate.

$$(C_6H_5)_2CHCOCOOCH_3 \xrightarrow{CH_3MgI} (C_6H_5)_2CHC(OH)(CH_3)COOCH_3$$

The melting point of the methyl ester of our acid agrees with that reported by Kohler and Weiner for α-methyl-β,β-diphenyllactate. Furthermore, the properties of our acid and its ethyl ester agree with those of the compounds described by Bardon and Ramart. In view of these facts, we believe that the acid obtained by Bardon and Ramart was identical with our acid, and this acid is α-methyl-β,β-diphenyllactic acid.

N-(β-Diethylaminoethyl)-diphenylacetamide.

N-(β-Diethylaminoethyl)-diphenylacetamide was first described as one of a series of basic amides having therapeutic properties by Meischer, Meisel and Hoffmann(78). According to these investigators, basic amides of this nature may be prepared "either by causing an aliphatic-aromatic acid, or a substitution product, derivative or equivalent of such an acid to react with a polyamine having at least one free amino H, or by causing an aliphatic-aromatic amide or substitution product to react with a reactive ester of an amino alcohol." They reported that the amide base and the hydrochloride salt melted at 94° and 144°, respectively.

Burtner and Cusic(56) prepared this basic amide, in the form of the hydrochloride, in the following manner and reported

(78) Meischer, Meisel and Hoffmann, U.S. Patent, 2,009,144; Chem. Abstracts, 29, 5993 (1935).

it to melt at 145°.

$$(C_6H_5)_2CHCOCl + H_2NCH_2CH_2N(C_2H_5)_2 \longrightarrow (C_6H_5)_2CHCONHCH_2CH_2N(C_2H_5)_2 \cdot HCl$$

Meier and Hoffman[79] reported on the antispasmodic activity and toxicity of both the hydrochloride and the methochloride of the basic amide.

We prepared N-(β-diethylaminoethyl)-diphenylacetamide by a new method, which we felt might be more advantageous than those employed by the above-mentioned investigators. We found that diphenylacetamide, prepared by the interaction of diphenylacetyl chloride and ammonia, reacted with sodamide to form a sodium derivative which, upon treatment with β-diethylaminoethyl chloride, was converted into N-(β-diethylaminoethyl)-diphenylacetamide in good yield.

$$(C_6H_5)_2CHCOOH \xrightarrow{SOCl_2} (C_6H_5)_2CHCOCl \xrightarrow{NH_3} (C_6H_5)_2CHCONH_2$$

$$(C_6H_5)_2CHCONH_2 \xrightarrow[2)\ ClCH_2CH_2N(C_2H_5)_2]{1)\ NaNH_2} (C_6H_5)_2CHCONHCH_2CH_2N(C_2H_5)_2$$

The melting points of both the base and the hydrochloride of our basic amide agreed with those previously reported for these compounds. Its structure was confirmed by its hydrolysis to diphenylacetic acid; had the basic alkyl group entered the α-position of diphenylacetamide, the hydrolysis product would have been α-(β-diethylaminoethyl)-diphenylacetic acid.

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(79) Meier and Hoffmann, Helv. med. Acta, 7, 106 (1941).

$$(C_6H_5)_2CHCONHCH_2CH_2N(C_2H_5)_2 \xrightarrow{\text{hydrolysis}} (C_6H_5)_2CHCOOH + H_2NCH_2CH_2N(C_2H_5)_2$$

$$(C_6H_5)_2C(CONH_2)CH_2CH_2N(C_2H_5)_2 \xrightarrow{\text{hydrolysis}} (C_6H_5)_2C(COOH)CH_2CH_2N(C_2H_5)_2 + NH_3$$

We also prepared the methobromide of our basic amide for pharmacological evaluation.

β,β-Diphenylacrylic Acid.

Initially, it was believed that the most practical method for the preparation of a basic-alkyl ester of β,β-diphenylglycidic acid might be the epoxidation of β-diethylaminoethyl β,β-diphenylacrylate*.

$$(C_6H_5)_2C{=}CHCOOCH_2CH_2N(C_2H_5)_2 \xrightarrow{\text{epoxidation}} (C_6H_5)_2C\overset{O}{\diagdown\diagup}CHCOOCH_2CH_2N(C_2H_5)_2$$

In order to prepare the required β,β-diphenylacrylic acid, we, at first, followed the procedure of Rupe and Busolt[60], which is outlined below.

$$(C_6H_5)_2CO \xrightarrow[BrCH_2COOC_2H_5]{Zn} (C_6H_5)_2C(OH)CH_2COOC_2H_5 \xrightarrow{\text{hydrolysis}} (C_6H_5)_2C(OH)CH_2COOH$$

$$(C_6H_5)_2C(OH)CH_2COOH \xrightarrow{\text{dehydration}} (C_6H_5)_2C{=}CHCOOH$$

---

* The preparation of this ester, in the form of the hydrochloride, had been described by Burtner and Cusic[56].

However, like other investigators[61,62], we encountered considerable difficulty in the dehydration of β,β-diphenyl-β-hydroxypropionic acid; several dehydration procedures were attempted but the yield from them was always low.

We found that, while the hydroxy acid was not readily dehydrated, its ethyl ester could be dehydrated, quantitatively, by means of hydrogen chloride in the general manner described by Natelson and Gottfried[64].

$$(C_6H_5)_2C(OH)CH_2COOC_2H_5 \xrightarrow[100°]{HCl} (C_6H_5)_2C{=}CHCOOC_2H_5$$

β,β-Diphenylacrylic acid was obtained by the hydrolysis of the ester, and was converted into its β-diethylaminoethyl ester by means of the Horenstein-Pählicke esterification[74].

Contrary to our expectations, we were unable to epoxidate the unsaturated basic ester. The procedure of Weitz and Scheffer[80], in which alkaline peroxide was employed, resulted in hydrolysis of the ester*. Perphthalic acid did not react with the ester; the initial ester was recovered unchanged from the reaction mixture. Experimentation along these lines was abandoned since we had simultaneously shown that β,β-diphenylglycidic acid could be isolated and esterified directly to form the desired basic-alkyl glycidic ester.

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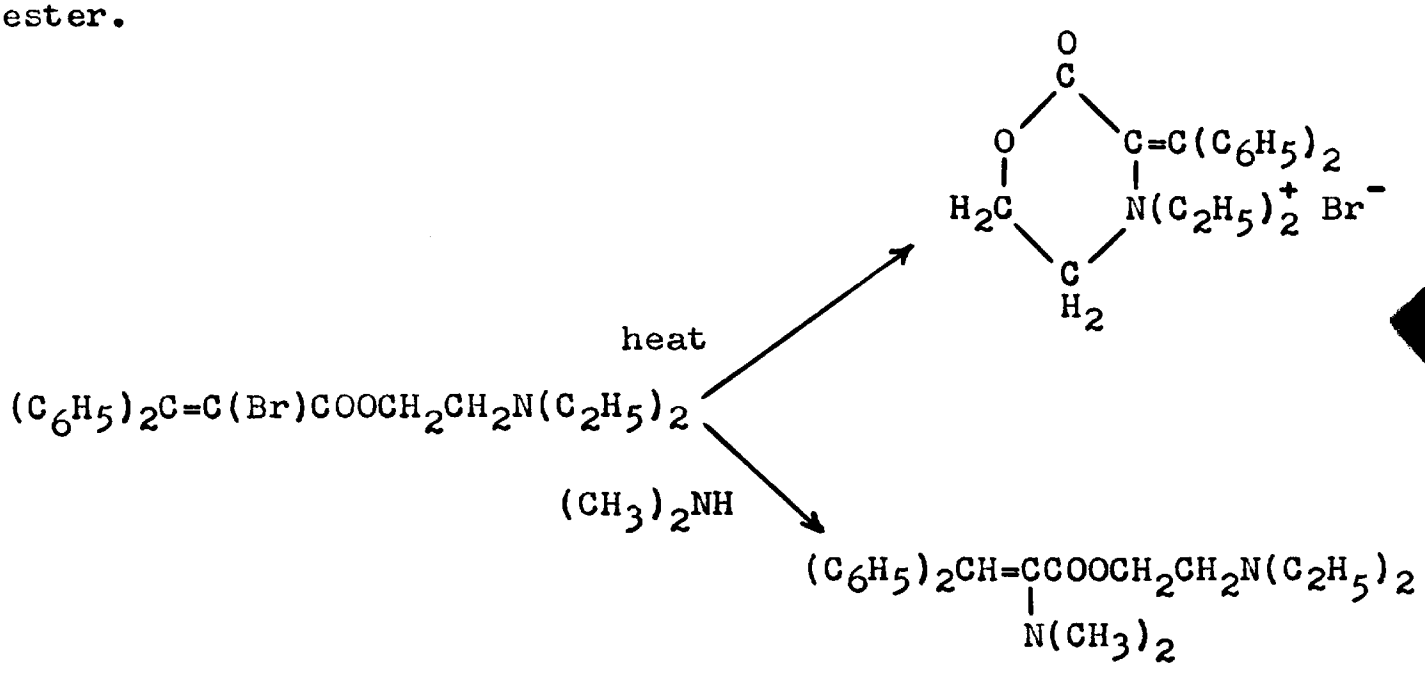
(80) Weitz and Scheffer, Ber., 54, 2327 (1921).

* This procedure was also applied to β,β-diphenylacrylic acid and was unsuccessful.

When our β-diethylaminoethyl β,β-diphenylacrylate was treated with bromine, hydrogen bromide was evolved, and the ester was converted into β-diethylaminoethyl α-bromo-β,β-diphenylacrylate.

$$(C_6H_5)_2C{=}CHCOOCH_2CH_2N(C_2H_5)_2 \xrightarrow{Br_2} (C_6H_5)_2C{=}C(Br)COOCH_2CH_2N(C_2H_5)_2$$

No dibromo compound, which might be expected to be formed by the addition of bromine to the double bond, was detected in the reaction product. The bromo ester showed unusual stability. It did not cyclize to form a morpholone upon distillation at 172-176° (0.01 mm.), and we were unable to react it with dimethylamine in an attempt to prepare the α-dimethylamino ester.

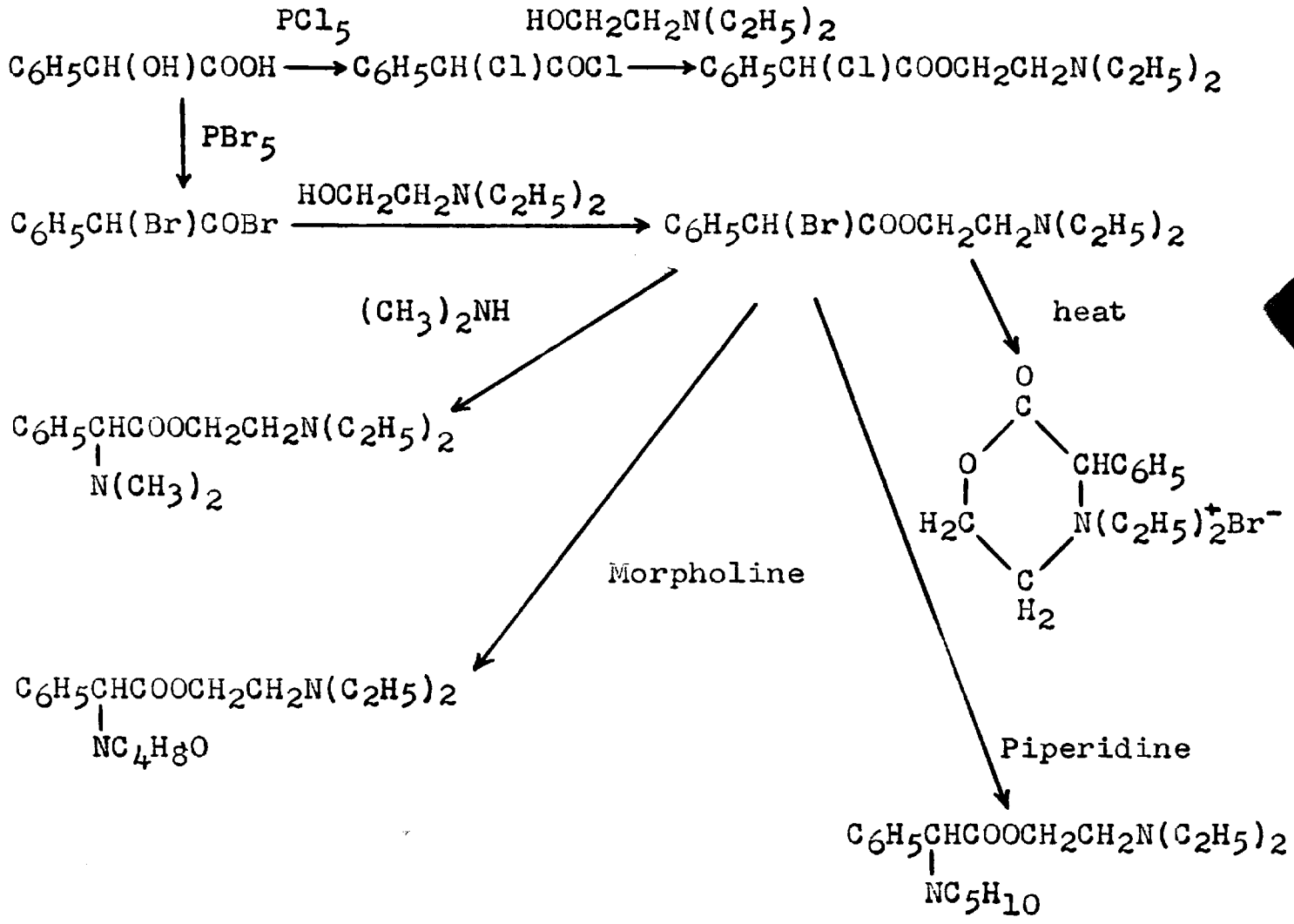


EXPERIMENTAL PART.

Preparation of the following compounds according to Scheme 1.

α-Chlorophenacetyl chloride.
β-Diethylaminoethyl α-chlorophenylacetate.
α-Bromophenacetyl bromide.
β-Diethylaminoethyl α-bromophenylacetate.
3-Phenyl-4-ethylmorpholone-2 ethobromide.
β-Diethylaminoethyl α-dimethylaminophenylacetate.
β-Diethylaminoethyl α-morpholinophenylacetate.
β-Diethylaminoethyl α-piperidinophenylacetate.

Scheme 1.



α-Chlorophenacetyl Chloride.- In a flask equipped with a condenser set for distillation, there was placed a mixture of 15.2 g. (0.1 mole) of mandelic acid and 41.6 g. (0.2 mole) of phosphorous pentachloride. A spontaneous, but not vigorous, reaction occurred within a few minutes. After the initial reaction had subsided, the mixture was heated for four hours by means of an oil-bath, the temperature of which was maintained at 120-140°. During this time, most of the phosphorous oxychloride, formed in the reaction, distilled from the liquid reaction mixture. Distillation of the residual material yielded 11.5 g. (61%) of the desired acid chloride, b.p. 108-110° (15-16 mm.)(81).

β-Diethylaminoethyl α-Chlorophenylacetate Hydrochloride.- To a stirred solution of 11.5 g. (0.061 mole) of α-chlorophenacetyl chloride in 150 cc. of anhydrous ether, there was added a solution of 7.2 g. (0.061 mole) of β-diethylaminoethanol in 50 cc. of anhydrous ether over a period of forty-five minutes. The ester hydrochloride separated as a solid during the addition, and after the reaction mixture had remained at room temperature for twelve hours, the solid was isolated by filtration and dried. The crude material weighed 16 g. (86%).

The crude salt was dissolved in water, the solution was made alkaline, and the liberated base was extracted with ether. After the ether solution had been repeatedly washed with water, it was dried over anhydrous magnesium sulfate, and filtered.

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(81) Staudinger, Ber., 44, 533 (1911), obtained this compound, b.p. 110° (14 mm.), by the same procedure.

Treatment of the filtrate with ethereal hydrogen chloride precipitated the hydrochloride salt which, after recrystallization from a mixture of acetone and ether, melted at 126-128°.

Anal. Calcd. for $C_{14}H_{21}Cl_2NO_2$: N, 4.57. Cl^-, 11.58.

Found: N, 4.49. Cl^-, 11.78.

α-Bromophenacetyl Bromide.- To phosphorous pentabromide, prepared by the gradual addition of 44.4 g. (0.278 mole) of bromine to 75.3 g. (0.278 mole) of phosphorous tribromide over a period of forty-five minutes(82), there was added 20.0 g. (0.13 mole) of mandelic acid. The mixture was gently warmed, and, when the initial reaction had subsided, the mixture was heated on a steam-bath for one and one-half hours. Direct distillation of the mixture yielded 24.0 g. (66.4%) of the desired acid bromide, b.p. 140-144° (25 mm.)(83).

The acid bromide was also prepared from the interaction of phenylacetic acid, phosphorous and bromine according to the directions of Anshütz, Hahn and Walter(71), but the yield was only 23%.

β-Diethylaminoethyl α-Bromophenylacetate Hydrobromide.- A solution of 6.9 g. (0.059 mole) of β-diethylaminoethyl alcohol in 50 cc. of anhydrous ether was added, over a period of one hour, to a stirred solution of 16.3 g. (0.059 mole) of α-bromophenacetyl bromide in 150 cc. of anhydrous ether. The reaction temperature was maintained at 25° during the addition. After the mixture had been stirred for an additional hour, the white solid, which had separated, was isolated by filtration,

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(82) This procedure was described by Carothers (J. Am. Chem. Soc., 48, 3192 (1926)).

(83) Cohen(72) reported 138-140° (15 mm.).

and dried; yield, 20 g. (86%). After four recrystallizations from an ethanol-ether mixture, the ester hydrobromide melted at 105-107°.

Anal. Calcd. for $C_{14}H_{21}Br_2NO_2$: N, 3.55. Br(total), 40.45.
Found: N, 3.58. Br(total), 40.88.

3-Phenyl-4-ethylmorpholone-2 Ethobromide.- A dry ether solution of β-diethylaminoethyl α-bromophenylacetate, which had been obtained from 5.0 g. of the corresponding hydrobromide salt, was evaporated to an oil at a low temperature. The oil partially solidified after it had been at room temperature for two days, and the oily solid was washed with ether in order to remove the oil. The solid was dissolved in ethanol, and the solution was treated with decolorizing charcoal. The solution was filtered, and the filtrate was diluted with anhydrous ether in order to precipitate the morpholone salt. There was obtained 1.2 g. (30%) of the quaternary compound, m.p. 191-192° after recrystallization from an ethanol-ether mixture.

Anal. Calcd. for $C_{14}H_{20}BrNO_2$: N, 4.46. Br^-, 25.43.
Found: N, 4.55. Br^-, 25.18.

β-Diethylaminoethyl α-Dimethylaminophenylacetate Dihydrochloride.- A mixture of 8.0 g. (0.025 mole) of β-diethylaminoethyl α-bromophenylacetate, 10 g. (0.22 mole) of anhydrous dimethylamine and 50 cc. of chloroform, contained in a stoppered citrate bottle, was heated on a steam-bath for five hours. The residue, which remained after the removal of the solvent, was treated with water, and the insoluble oil was extracted

with ether. The ether solution was washed with water, dried over anhydrous magnesium sulfate, and the ether was removed by distillation. The residue was then distilled; yield, 4.7 g. (67.5%); b.p. 104-107° (0.1 mm.).

The dihydrochloride salt of the above ester was prepared by the treatment of an ether solution of the ester with ethereal hydrogen chloride. The precipitated salt was isolated by filtration, and recrystallized from a mixture of ethanol and ether; yield, 4.0 g. (80%); m.p. 194-195° (dec.).

Anal. Calcd. for $C_{16}H_{28}Cl_2N_2O_2$: N, 7.98. Cl^-, 20.18.
Found: N, 7.98. Cl^-, 20.29.

β-Diethylaminoethyl α-Morpholinophenylacetate.- When 10.5 g. (0.12 mole) of morpholine was added to a solution of 8.0 g. (0.025 mole) of crude β-diethylaminoethyl α-bromophenylacetate in 50 cc. of chloroform, a solid separated almost immediately. The mixture was heated on a steam-bath for five hours, water was added, and the layers were separated. The aqueous layer was extracted once with ether, and the ether solution was added to the chloroform layer. The solvent was removed, and the residue was distilled; yield, 7.0 g. (86%); b.p. 129-132° (0.01 mm.).

The dihydrochloride of the above ester, prepared by the addition of excess ethereal hydrogen chloride to a solution of 3.8 g. (0.012 mole) of the base dissolved in anhydrous ether, melted at 170-171° after recrystallization from a mixture of ethanol and ether. The yield was 4.3 g. (91%).

Anal. Calcd. for $C_{18}H_{30}Cl_2N_2O_3$: N, 7.12. Cl^-, 18.03.
Found: N, 7.25. Cl^-, 17.77

The methobromide was prepared as follows: A solution of 3.2 g. (0.01 mole) of the base and 0.95 g. (0.01 mole) of methyl bromide in chloroform was allowed to remain at room temperature for two days. The solvent was removed, the oily residue was converted into a solid by ether trituration, and the solid was recrystallized from a mixture of isopropyl alcohol and ether. There was obtained 2.6 g. (62.5%) of the quaternary compound, m.p. 144-146°.

Anal. Calcd. for $C_{19}H_{31}BrN_2O_3$: N, 6.75. Br^-, 19.24.
Found: N, 6.84. Br^-, 19.39.

β-Diethylaminoethyl α-Piperidinophenylacetate Dihydrochloride.- A solution of 6.3 g. (0.02 mole) of crude β-diethylaminoethyl α-bromophenylacetate and 10.0 g. (0.12 mole) of piperidine in 50 cc. of chloroform was heated on a steam-bath for seven hours. The semi-solid residue, which remained after the removal of the solvent, was treated with water, and the insoluble oil was extracted with ether. The ether solution was washed with water, dried over anhydrous magnesium sulfate, and the ether was removed. The residue was distilled: yield, 5.0 g. (78%); b.p. 132-136° (0.01 mm.).

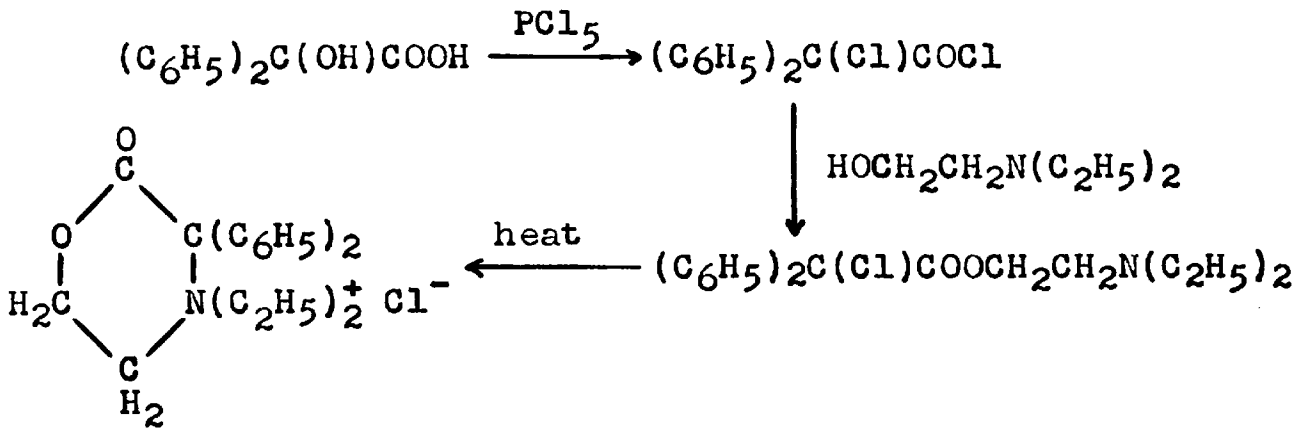
When an ethereal solution of 3.0 g. of the ester base was treated with excess ethereal hydrogen chloride, the dihydrochloride salt separated as a solid. The salt was isolated by filtration, and recrystallized from a mixture of ethanol and ether; yield, 3.0 g. (81%); m.p. 194-195°.

Anal. Calcd. for $C_{19}H_{32}Cl_2N_2O_2$: N, 7.16. Cl^-, 18.12.
Found: N, 7.20. Cl^-, 18.18.

Preparation of the following compounds according to Scheme 2.

α-Chlorodiphenylacetyl chloride.
β-Diethylaminoethyl α-chlorodiphenylacetate.
3,3-Diphenyl-4-ethylmorpholone-2 ethochloride.

Scheme 2.



α-Chlorodiphenylacetyl Chloride.- A spontaneous reaction occurred when 22.8 g. (0.1 mole) of benzilic acid was mixed with 41.6 g. (0.2 mole) of phosphorous pentachloride at room temperature. After the initial reaction had subsided, the mixture was heated at 120-130° for one hour, after which the volatile products were removed by vacuum distillation. The oily residue was poured into ice-water whereupon the oil solidified, and the solid was collected on a filter. The moist solid was dissolved in 30 cc. of petroleum ether (60-70°), and the solution was decanted from the residual water through a filter. The acid chloride crystallized from the cooled filtrate, was isolated by filtration, and dried; yield, 16.1 g. (60.8%);

m.p. 49-50°(84).

β-Diethylaminoethyl α-Chlorodiphenylacetate Hydrochloride.- A solution of 7.2 g. (0.06 mole) of β-diethylaminoethanol in 20 cc. of benzene was added, dropwise, over a period of thrity minutes to a stirred solution of 16.1 g. (0.06 mole) of α-chlorodiphenylacetyl chloride in 100 cc. of benzene. The reaction temperature was maintained at 25-35° during this time. The solvent was removed by distillation, and the oily residue, which solidified, was triturated with a small volume of acetone, and isolated by filtration. That material, which dissolved in the acetone, was largely recovered by the concentration of the filtrate; yield of crude material, 16.7 g. (72%).

In order to purify the ester hydrochloride, it was necessary to liberate the ester base, dissolve it in ether, and wash the ether solution with several portions of water. The dried ether solution was then treated with ethereal hydrogen chloride, and the precipitated hydrochloride was recrystallized from acetone; m.p. 152.5-153.5°(85).

3,3-Diphenyl-4-ethylmorpholone-2 Ethochloride.- An aqueous solution of 11.4 g. of β-diethylaminoethyl α-chlorodiphenylacetate hydrochloride was covered with ether, and made alkaline with dilute sodium hydroxide solution. The liberated base was extracted with ether, the ether solution was washed with water, and dried over anhydrous magnesium sulfate. The ether

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(84) Bickel(73) employed the same procedure, and reported the melting point to be 50°.

(85) Burtner and Cusic(56) found 149-151°, and stated that the salt could not be recrystallized.

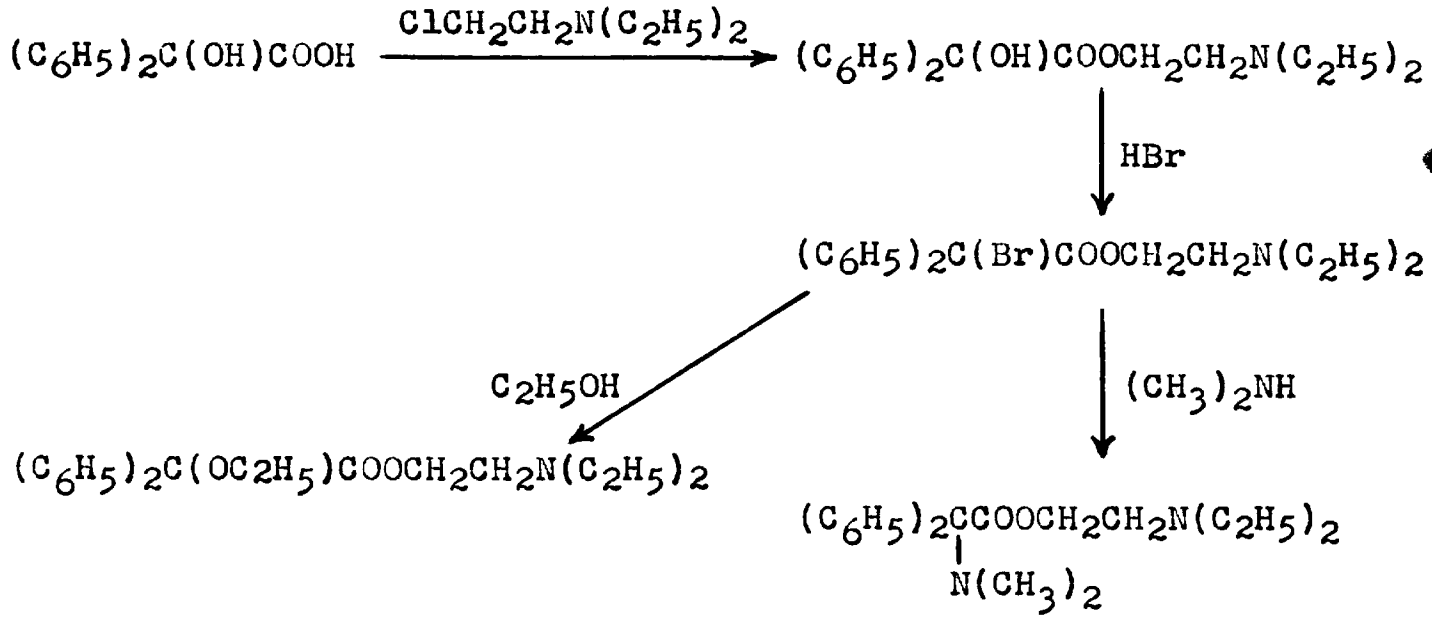
was removed, and the oily residue (6.2 g.) was heated on a steam-bath for twenty-four hours. The dark, brown mixture was dissolved in ethanol, the solution was treated with Norite, filtered, and the solvent was removed. Trituration of the oily residue converted it into a tan powder (1.0 g.; 16%) which was recrystallized from a mixture of isopropyl alcohol and ether; m.p. 177-179°.

Anal. Calcd. for $C_{20}H_{24}ClNO_2$: N, 4.05. Cl^-, 10.25.
Found: N, 4.14. Cl^-, 10.44.

Preparation of the following compounds according to Scheme 3.

β-Diethylaminoethyl α-bromodiphenylacetate.
β-Diethylaminoethyl α-ethoxydiphenylacetate.
β-Diethylaminoethyl α-dimethylaminodiphenylacetate.

Scheme 3.



β-Diethylaminoethyl α-Bromodiphenylacetate Hydrobromide.- A suspension of 3.64 g. (0.01 mole) of β-diethylaminoethyl benzilate hydrochloride[74] in 35 cc. of chloroform was cooled in an ice-bath, and saturated with hydrogen bromide. The resulting homogeneous solution was allowed to remain at 0-10° for nineteen hours, and at room temperature for an additional ten hours, after which the solvent was removed under reduced pressure. The oily residue soon solidified, and was recrystallized from a mixture of chloroform and ether; yield, 4.3 g. (91.2%); m.p. 164-165°.

Anal. Calcd. for $C_{20}H_{25}Br_2NO_2$: N, 2.97. Br(total), 33.92.
Found: N, 3.12. Br(total), 34.20.

β-Diethylaminoethyl α-Ethoxydiphenylacetate Hydrobromide.- A solution of 2.36 g. (0.005 mole) of β-diethylaminoethyl α-bromodiphenylacetate hydrobromide in 50 cc. of absolute ethanol was refluxed for one hour. The solution was then concentrated to approximately 15 cc. and diluted with four volumes of anhydrous ether. The solid, which separated, was collected on a filter, washed and dried; yield, 1.9 g. (87%); m.p. 150-151°.

Anal. Calcd. for $C_{22}H_{30}BrNO_3$: N, 3.21. Br^-, 18.32.
Found: N, 3.15. Br^-, 18.28.

β-Diethylaminoethyl α-Dimethylaminodiphenylacetate.- A homogeneous mixture of 3.3 g. (0.007 mole) of β-diethylaminoethyl α-bromodiphenylacetate, 8.0 g. (0.18 mole) of anhydrous dimethylamine and 50 cc. of chloroform, contained in a stoppered citrate bottle, was heated on a steam-bath for five hours.

The solvent was removed by vacuum distillation, and the semi-solid residue was treated with water. The insoluble oil was extracted with ether, the ether solution was washed with water and dried over anhydrous magnesium sulfate. After the removal of the ether, the residue was distilled; yield, 1.7 g. (68%); b.p. 152-154° (0.01 mm.).

The addition of the calculated amount of ethereal hydrogen chloride to an ether solution of the above base precipitated 1.8 g. (96%) of the monohydrochloride, m.p. 182-183° (dec.) after recrystallization from acetone.

Anal. Calcd. for $C_{22}H_{31}ClN_2O_2$: N, 7.17. Cl^-, 9.08.
Found: N, 7.09. Cl^-, 9.15.

The following procedure was used to prepare the methobromide of this ester: three grams of the base, dissolved in 25 cc. of chloroform, was treated with one equivalent of methyl bromide, and the homogeneous solution was allowed to remain at room temperature for two days. The oil, which remained after the removal of the solvent, was converted into a solid by trituration under anhydrous ether. After recrystallization of the solid from acetone, there was obtained 1.4 g. (37%) of the pure quaternary compound, m.p. 190-192° (dec.).

Anal. Calcd. for $C_{23}H_{33}BrN_2O_2$: N, 6.24. Br^-, 17.78.
Found: N, 6.28. Br^-, 17.53.

Preparation of the following compounds:

Ethyl β,β-diphenylglycidate.
β,β-Diphenylglycidic acid.
Ethyl diphenylpyruvate.
Diphenylpyruvic acid.
β,β-Diphenylglycidamide.
Diphenylpyruvamide.
β-Diethylaminoethyl β,β-diphenylglycidate.
Methyl β,β-diphenylglycidate.
Methyl diphenylpyruvate.
Ethyl β,β-diphenylglycerate.
β,β-Diphenylglyceric acid.
β,β-Diphenylglyceramide.
β-Diethylaminoethyl β,β-diphenylglycerate.
β,β-Diphenylglycidonitrile.
Ethyl β,β-diphenylglycidimino ethyl ether hydrochloride.
β-Diethylaminoethyl α-chloroacetate.
4-Ethylmorpholone-2 ethochloride.

Ethyl β,β-Diphenylglycidate.- To a stirred solution of 91 g. (0.5 mole) of benzophenone and 61.5 g. (0.5 mole) of ethyl chloroacetate in 150 cc. of anhydrous ether there was added 38 g. (0.56 mole) of powdered sodium ethylate* over a period of four and one-half hours. The reaction temperature was maintained at 0-4° during the addition. After the reaction mixture had been stirred at room temperature for twelve hours, the ether was removed, and the thick, brown residue was stirred

* Alcohol-free sodium ethylate was prepared as follows: A weighed amount of sodium was reacted with absolute ethanol, and the solution was vacuum-distilled to dryness. The solid residue ($C_2H_5ONa \cdot 2C_2H_5OH$) was then heated, in vacuo, by means of an oil-bath, the temperature of which was maintained at 200-225°, until it had attained constant weight. Since hot sodium ethylate is rapidly decomposed by air, it was important to maintain the vacuum until the sodium ethylate had cooled to room temperature.

at 100° for an additional six hours. The cooled mass was acidified with 20 cc. of glacial acetic acid, and poured into 400 cc. of ice-water. The insoluble oil was extracted with ether, and the ether solution was washed with water and dilute sodium bicarbonate solution until the washings were slightly alkaline. After the ether solution had been dried over anhydrous magnesium sulfate, the ether was removed and the residue was distilled. There was obtained 27.5 g. of unreacted benzophenone, b.p. 123-129° (1 mm.), and 89 g. of a yellow oil, b.p. 151-160° (1 mm.), which nearly completely solidified when cooled. Recrystallization of this mixture from 50 cc. of ethanol yielded 64 g. (47.8%) of the desired glycidic ester, m.p. 48-49°(86). The boiling point of the pure ester is 152-153° (1 mm.), and it may be distilled unchanged at 190-193° (11 mm.)

Redistillation of the alcoholic mother liquor from the recrystallization of the glycidic ester yielded 19 g. of an oil, b.p. 153-159° (1 mm.) from which there was obtained, by hydrolysis, 9.9 g. (54%) of sodium diphenylpyruvate. Acidification of an aqueous solution of this salt precipitated 7.2 g. (74%) of diphenylpyruvic acid monohydrate, m.p. 85-87°. In order to obtain the anhydrous acid, the monohydrate was dissolved in chloroform, the solution was refluxed for fifteen minutes after which the solvent was removed by vacuum

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(86) Pointet(38), as well as Rutowski and Dajew(36) found 47°.

distillation. The solid residue was recrystallized from a mixture of chloroform and petroleum ether (60-70°); yield, 5.3 g. (79%); m.p. 116-117°.

β,β-Diphenylglycidic Acid.- Eighteen and eight-tenths grams (0.07 mole) of ethyl β,β-diphenylglycidate were dissolved in a cold solution of sodium ethylate, prepared from 1.6 g. (0.07 g. atom) of sodium and 50 cc. of absolute alcohol. The cold solution was then treated with 1.3 cc. (0.07 mole) of water, and allowed to remain at room temperature for twelve hours. The sodium salt, which had separated, was collected on a filter, washed with cold alcohol, and dried; yield, 16 g. (87%).

In order to liberate the free acid, 5.2 g. of the above salt was dissolved in cold water, and the solution was covered with ether. Cold, dilute hydrochloric acid was then added to the stirred mixture until the aqueous layer was acidic. The layers were separated, the ether layer was dried over anhydrous magnesium sulfate, and the ether was removed at a low temperature. The residual solid (3.9 g.; 81.3%) was recrystallized from a mixture of ether and petroleum ether (30-60°); m.p. 70-71° (dec.).

When the glycidic acid was heated at its melting point until gas evolution had ceased, and the residual oil was distilled, diphenylacetaldehyde, b.p. 170-174° (16 mm.), was obtained in 75.5% yield. The aldehyde was identified by means of its semicarbazone, m.p. 160-161°[87].

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(87) Daniloff and Venus-Danilova[54] reported 160.5°.

Ethyl Diphenylpyruvate.- Eighteen and eight-tenths grams (0.07 mole) of ethyl β,β-diphenylglycidate were maintained at 200° for forty-five minutes while a slow stream of hydrogen chloride was bubbled through the molten ester. The oil was then distilled; yield, 16.5 g. (88.2%); b.p. 152-155° (1 mm.).

The oily ester would not crystallize until it had been innoculated with seed crystals which were obtained in the following manner: An alcoholic solution of diphenylpyruvic acid was treated with a slight excess of alcoholic silver nitrate whereupon the silver salt of the acid separated. The salt was isolated, treated with an excess of ethyl iodide, and the mixture was refluxed for three hours. After the mixture was filtered, it was distilled and the distilled ester solidified after it had been in a refrigerator for one day. The solid ester melted at 36-37° after recrystallization from a mixture of ether and petroleum ether (30-60°)(88).

The phenylhydrazone of the pyruvic ester, prepared from the ester and phenylhydrazine hydrochloride, melted at 101-102°(89) after recrystallization from ethanol.

Diphenylpyruvic Acid.- To a cold solution of 4.0 g. (0.175 g. atom) of sodium in 150 cc. of absolute ethanol there was added 43.7 g. (0.17 mole) of ethyl diphenylpyruvate and 3.5 cc. (0.19 mole) of water. The solution was placed in an ice-bath for four hours, and the precipitated sodium diphenylpyruvate was collected on a filter, washed with ethanol,

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(88) Kohler, Richtmyer and Hester(41) reported 37°.
(89) Kohler, Richtmyer, and Hester(41) found 99-100°.

and dissolved in 600 cc. of water. The solution was acidified with hydrochloric acid, filtered, and the solid acid was washed with water and dried. There was obtained 38 g. (87%) of diphenylpyruvic acid monohydrate, m.p. 85-87°, after recrystallization from water.

Anal. Calcd. for $C_{15}H_{14}O_4$: Neut. Equiv., 258.3.
Found: Neut. Equiv., 255.2.

In order to obtain the anhydrous acid, the monohydrate was dissolved in 100 cc. of chloroform, and the solution was refluxed for fifteen minutes. The solvent was removed, and the solid residue was recrystallized from a mixture of chloroform and petroleum ether; yield, 32.6 g. (80.1%, based on the amount of initial ester used); m.p. 116-117°. Recrystallization of this acid from water converted it into the corresponding monohydrate.

Anal. Calcd. for $C_{15}H_{12}O_3$: Neut. Equiv., 240.3.
Found: Neut. Equiv., 242.1.

The phenylhydrazone of the above acid melted at 208° (dec.)[90]. The acid was converted by vacuum distillation into diphenylacetic acid, m.p. 143-145°.

β,β-Diphenylglycidamide.- A solution of 4.0 g. (0.015 mole) of ethyl β,β-diphenylglycidate in 40 cc. of ethanol was treated with 25 cc. of 28% aqueous ammonia, and the solution was allowed to remain at room temperature for three days. It was then

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(90) Troell[39] reported 189° (dec.); Kohler, Richtmyer and Hester[41] found 210° or 245° depending upon the rate of heating.

cooled, saturated with ammonia, and allowed to remain at room temperature for an additional day. The solution, from which white needles had separated, was concentrated somewhat, and the solid was isolated, washed and dried; yield, 2.0 g. (55.8%); m.p. 148-149° after recrystallization from 95% ethanol.

Anal. Calcd. for $C_{15}H_{13}NO_2$: N, 5.86.

Found: N, 5.83.

It was found possible to rearrange β,β-diphenylglycidamide to diphenylpyruvamide in the following manner: 0.2 g. of the glycidamide was heated at 175° for five minutes in the presence of hydrogen chloride. The oil solidified, when cooled, and was recrystallized from ethanol; yield, 0.15 g. (75%); m.p. 166-168°. There was no depression in the melting point when this material was mixed with authentic diphenylpyruvamide.

Diphenylpyruvamide.- To a solution of 4.0 g. (0.015 mole) of ethyl diphenylpyruvate in 25 cc. of ethanol there was added 25 cc. of 28% aqueous ammonia. A white solid separated almost immediately and, after the mixture had been at room temperature overnight, the solid was collected on a filter, washed with ethanol and dried. There was obtained 3.2 g. (89.2%) of diphenylpyruvamide*, m.p. 167-168° after recrystallization from 95% ethanol.

Anal. Calcd. for $C_{15}H_{13}NO_2$: N, 5.86.

Found: N, 5.78.

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* This amide was also prepared by the interaction of diphenylpyruvyl chloride and ammonia.

Reaction between Diphenylpyruvic Acid and β-Diethylaminoethyl Chloride in Alcohol.- A homogeneous mixture of 4.8 g. (0.02 mole) of diphenylpyruvic acid, 2.7 g. (0.02 mole) of β-diethylaminoethyl chloride and 30 cc. of absolute ethanol was refluxed for six hours after which the solvent was removed. The residual oil was converted, in part, into a crystalline solid by trituration under anhydrous ether, and the solid was collected on a filter, washed with ether and dried. This solid (3.0 g.; 88.6%) was β-diethylaminoethanol hydrochloride, m.p. 135-136°(91). There was no depression in its melting point when it was mixed with an authentic sample.

Anal. Calcd. for $C_6H_{16}ClNO$: N, 9.12. Cl^-, 23.07.

Found: N, 8.84. Cl^-, 23.27.

The ether solution, from the trituration and filtration of the above salt, was evaporated, and the residual oil (5.5 g.; 103%) was distilled; b.p. 153-155° (1 mm.). It was identified as ethyl diphenylpyruvate by its phenylhydrazone, m.p. 100-101°, and by its hydrolysis to diphenylpyruvic acid, m.p. 116-117°, in 80% yield.

β-Diethylaminoethyl β,β-Diphenylglycidate Hydrochloride.- A dry ether solution of β,β-diphenylglycidic acid, liberated from 7.9 g. (0.03 mole) of its sodium salt, was added to a dry ether solution of β-diethylaminoethyl chloride, obtained from 6.9 g. (0.04 mole) of the corresponding hydrochloride. The solution was distilled to one-half volume, 85 cc. of

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(91) Blicke and Maxwell(5) and Fenwick and Gilman (J. Biol. Chem., 84, 605 (1929)) reported 134-135°.

isopropyl alcohol were added, and the solution was distilled to remove the remainder of the ether. After the solution had been refluxed for twelve hours, it was filtered, and the filtrate was evaporated to an oil. The oil solidified upon trituration with ether, and the solid was recrystallized from a mixture of acetone and ethanol; yield, 3.5 g. (31%); m.p. 155-156°.

Anal. Calcd. for $C_{21}H_{26}ClNO_3$: N, 3.73. Cl^-, 9.43.
Found: N, 3.71. Cl^-, 9.59.

Methyl β,β-Diphenylglycidate.- A stirred solution of 36.4 g. (0.2 mole) of benzophenone and 21.7 g. (0.2 mole) of methyl chloroacetate in 200 cc. of anhydrous ether was treated with 8.2 g. (0.21 mole) of powdered sodamide, in small portions, over a period of one hour. The temperature of the reaction mixture was maintained at 0-5° during the addition. The mixture was then stirred at approximately 10° for six hours after which it was allowed to remain at room temperature for twelve hours. The mixture was poured into 200 cc. of ice-water, the layers were separated and the aqueous layer was extracted with ether. The combined ether solutions were washed with water, dried over anhydrous magnesium sulfate and the ether was removed by distillation. The residue was then distilled; yield, 7.0 g. (14%); b.p. 165-167° (5 mm.). The distillate solidified, and melted at 53-54° after recrystallization from methanol.

Anal. Calcd. for $C_{16}H_{14}O_3$: C, 75.57. H, 5.55.
Found: C, 75.35. H, 5.24.

Methyl Diphenylpyruvate.- (Method A) A mixture of 1.2 g. (0.005 mole) of diphenylpyruvic acid, 1.0 g. of hydrogen chloride, and 25 cc. of absolute methanol was refluxed for three hours. The solution was then concentrated to approximately 3 cc., cooled, and the precipitated ester was isolated by filtration; yield, 0.7 g.; m.p. 69-70°[92] after recrystallization from methanol.

The esterification was also effected without the mineral acid catalyst, but the yield was only 18%.

(Method B) Methyl β,β-Diphenylglycidate (0.7 g.; 0.003 mole) was maintained at 200° for forty-five minutes while a slow stream of hydrogen chloride was bubbled through the molten ester. The oil solidified when cooled, and the solid was recrystallized from methanol; yield, 0.45 g. (64.3%), m.p. 69-70°.

(Method C) A small sample of diphenylpyruvic acid was warmed with thionyl chloride for a few minutes, and the thionyl chloride was removed. The residual oil, diphenylpyruvyl chloride, was then treated with absolute methanol at room temperature. The solvent was removed, and the residue was recrystallized from methanol; m.p. 66-68°.

Ethyl β,β-Diphenylglycerate.- Five and four-tenths grams (0.02 mole) of ethyl β,β-diphenylglycidate were suspended in 70 cc. of water, which had been acidified with hydrochloric acid, and the suspension was stirred and refluxed for one hour.

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(92) Kohler, Richtmyer and Hester[41] found 75°.

The suspended oil solidified when the mixture had cooled, and the solid was isolated by filtration; yield, 5.5 g. (91%); m.p. 130-131°[93] after recrystallization from ethanol.

β,β-Diphenylglyceric Acid.- To a solution of 8.9 g. (0.084 mole) of sodium carbonate in 100 cc. of water there was added 12 g. (0.042 mole) of ethyl β,β-diphenylglycerate, and the suspension was stirred and refluxed for one-half hour. The mixture was still heterogeneous and, when cooled, the insoluble oil solidified. The solid was collected on a filter, and dried; it weighed 4.7 g. and was evidently a mixture, the components of which were not identified. Acidification of the alkaline filtrate, which had previously been clarified by an ether extraction, precipitated the glyceric acid which was isolated by filtration; yield, 4.9 g. (45%); m.p. 177-178° (dec.) after recrystallization from dilute ethanol.

Anal. Calcd. for $C_{15}H_{14}O_4$: Neut. Equiv., 258.3.

Found: Neut. Equiv., 259.3.

β,β-Diphenylglyceramide.- A homogeneous solution of 2.9 g. (0.01 mole) of ethyl β,β-diphenylglycerate, 14 cc. (0.2 mole) of 28% aqueous ammonia in 50 cc. of ethanol was allowed to remain at room temperature for ten days. The solvent was removed under reduced pressure, and the solid residue was recrystallized from a mixture of ethyl acetate and petroleum ether (60-70°). The yield was 1.0 g. (38.6%); m.p. 173-174°.

Anal. Calcd. for $C_{15}H_{15}NO_3$: N, 5.45.

Found: N, 5.29.

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(93) Kohler and his associates[41] reported 130°.

β-Diethylaminoethyl β,β-Diphenylglycerate Hydrochloride.- A solution of 3.5 g. (0.013 mole) of β,β-diphenylglyceric acid and 1.8 g. (0.013 mole) of β-diethylaminoethyl chloride in 35 cc. of isopropyl alcohol was refluxed for eight and one-half hours. Some of the ester salt separated from the solution during this time. The mixture was cooled, filtered and the solid ester hydrochloride was recrystallized from ethanol; yield, 3.6 g. (70%); m.p. 194-195° (dec.).

Anal. Calcd. for $C_{21}H_{28}ClNO_4$: N, 3.56. Cl^-, 9.02.

Found: N, 3.47. Cl^-, 8.94.

Action of Phenylmagnesium Bromide on Ethyl β,β-Diphenylglycidate.- A solution of phenylmagnesium bromide, prepared from 2.4 g. (0.1 mole) of magnesium, 15.7 g. (0.1 mole) of bromobenzene and 85 cc. of anhydrous ether, was added, dropwise, to a stirred solution of 5.4 g. (0.02 mole) of ethyl β,β-diphenylglycidate in 100 cc. of anhydrous ether over a period of twenty-five minutes. During the addition of the Grignard reagent, the temperature of the reaction mixture was maintained at 20°. After the mixture had been stirred at 20-25° for three hours, and refluxed for one-half hour, it was decomposed with dilute hydrochloric acid. The layers were separated, and the ether layer was washed successively with dilute, aqueous sodium bicarbonate and water, after which the solvent was removed by distillation. The oily residue (10.9 g.) was then steam-distilled, and the distillate contained a small amount of biphenyl, m.p. 66-68°. Distillation of the residue from the steam-distillation yielded diphenylacetaldehyde, b.p. 135-150° (2 mm.), which was identified by means of its semicarbazone,

and a substance, b.p. 170-195° (2-3 mm.), which partially solidified. After recrystallization from a mixture of benzene and petroleum ether (60-70°), this material melted at 159-161°, and was shown to be triphenylcarbinol by a mixed melting point.

Action of Phenylmagnesium Bromide on β,β-Diphenylglycidic Acid.- A solution of phenylmagnesium bromide, prepared from 0.8 g. (0.033 mole) of magnesium, 5.0 g. (0.033 mole) of bromobenzene, and 50 cc. of anhydrous ether, was added, dropwise, to a stirred solution of 3.6 g. (0.015 mole) of β,β-diphenylglycidic acid in 60 cc. of anhydrous ether over a period of thirty-five minutes. The temperature of the reaction mixture was maintained at 10-15° during the addition. After it had been stirred at room temperature for an additional hour, the white suspension was decomposed by the slow addition of a cold solution of 5 cc. of concentrated hydrochloric acid in 35 cc. of water. The separated ether layer was washed with water, and then dried over anhydrous magnesium sulfate. After the removal of the ether, a brownish-yellow oil was obtained; yield, 4.3 g. The oil was dissolved in ether and the solution was extracted with dilute, aqueous sodium bicarbonate. The ether layer was treated in the manner described below. Acidification of the alkaline aqueous layer precipitated a white solid which weighed 1.2 g., and melted at 84-86° after recrystallization from water. It was shown to be diphenylpyruvic acid monohydrate by a mixed melting point, and by its dehydration to the anhydrous acid, m.p. 116-117°.

The ether layer was dried, and the solvent was removed; the oily residue (2.5 g.) boiled at approximately 130° (2-3 mm.), and was identified as diphenylacetaldehyde by means of its semicarbazone, m.p. 160-161°.

In an effort to determine the nature of the products formed by the interaction of an excess of the Grignard reagent and the acid at 25°, the above experiment was repeated using 1.9 g. (0.077 mole) of magnesium, 12.1 g. (0.077 mole) of bromobenzene and 3.6 g. (0.015 mole) of the glycidic acid. Diphenylpyruvic acid monohydrate (1.4 g.), and a small amount of biphenyl were isolated from the reaction mixture, and identified. In addition to these substances, there was obtained 3.0 g. of an oil which could not be distilled, and was not identified.

β,β-Diphenylglycidonitrile.- Twenty-eight grams (0.4 mole) of powdered sodium ethylate were added, in small portions, to a stirred solution of 72.9 g. (0.4 mole) of benzophenone and 30.2 g. (0.4 mole) of chloroacetonitrile in 150 cc. of anhydrous ether. The sodium ethylate was added over a period of four hours, and the temperature of the reaction mixture was maintained at 0-2° during this time. The reaction mixture was allowed to remain at room temperature overnight after which the solvent was removed; the dark, brown residue was then stirred at 75-80° for two hours. After the mass had cooled, it was covered with ether, treated with a solution of 10 cc. of glacial acetic acid in 150 cc. of water, and the mixture was stirred until most of the material had dissolved.

After filtration, the layers were separated, the aqueous layer was extracted with ether and the ether solutions were combined. The ether solution was washed with water, then with dilute sodium bicarbonate until the washings were slightly alkaline, and dried over anhydrous magnesium sulfate. The ether was removed, and the residue distilled. There was obtained 74 g. (84%) of a colorless oil; b.p. 124-126° (0.01 mm.). The oil darkened slowly at room temperature.

Anal. Calcd. for $C_{15}H_{11}NO$: N, 6.33.

Found: N, 5.53.

Ethyl β,β-Diphenylglycidimino Ethyl Ether Hydrochloride.- A mixture of 2.21 g. (0.01 mole) of β,β-diphenylglycidonitrile, 0.46 g. (0.01 mole) of absolute ethanol, 0.37 g. (0.01 mole) of hydrogen chloride and 45 cc. of anhydrous ether was allowed to remain in a refrigerator for five hours. The white solid, which had separated, was collected on a filter, washed with dry ether and dried; yield, 1.4 g. (46%); m.p. 108-109° (dec.).

Anal. Calcd. for $C_{17}H_{18}ClNO_2$: N, 4.61.

Found: N, 4.56.

When 0.1 g. of the above material was dissolved in water, an oil separated almost simultaneously. The oil solidified, when cooled, and the solid melted at 47-49°, after recrystallization from ethanol. There was no depression of the melting point when the solid was mixed with an authentic sample of ethyl β,β-diphenylglycidate.

When heated at 120-140° until gas evolution had ceased (5-10 min.), the imino ether salt was converted into

diphenylpyruvamide, m.p. 167-168°, after recrystallization from ethanol. There was no depression in the melting point when the material was mixed with an authentic sample of diphenylpyruvamide.

β-Diethylaminoethyl α-Chloroacetate.- To a stirred solution of 33.9 g. (0.3 mole) of chloroacetyl chloride in 150 cc. of dry benzene, maintained at 10-20°, there was added 36.3 g. (0.31 mole) of β-diethylaminoethyl alcohol in 50 cc. of benzene over a period of forty-five minutes. The resulting suspension was stirred at room temperature for an additional hour, after which it was diluted with 100 cc. of dry ether, and quickly filtered. The tan salt was extremely hygroscopic and was dried in a vacuum desiccator; yield, 66 g. (96%). None of the attempts, made to purify it by recrystallization from various solvents, was successful.

In order to obtain the free base, 23 g. (0.1 mole) of the crude salt was stirred into 15 cc. of 50% aqueous sodium hydroxide, which had been previously covered with ether and cooled to 10°. After the ether layer had been decanted, the aqueous solution was extracted with ether, and the ether solution was combined with the ether layer. The ether solution was dried over anhydrous magnesium sulfate, the ether was removed and the residue was distilled; b.p. 74-76° (2 mm.); yield, 5.0 g. (26%).

4-Ethylmorpholone-2 Ethochloride.- Five grams of β-diethylaminoethyl α-chloroacetate were allowed to remain at room temperature for four days after which the semi-solid mass was heated for one hour at 100° in order to complete

the cyclization. The mixture was dissolved in hot isopropyl alcohol and the solution was cooled whereupon 2.0 g. (40%) of shiny platelets separated; m.p. 198-199° after recrystallization from the same solvent. The morpholone quaternary salt was slightly hygroscopic.

Anal. Calcd. for $C_8H_{16}ClNO_2$: Cl^-, 18.31.

Found: Cl^-, 18.39.

Preparation of the following compounds:

Ethyl mandelate.
Ethyl α-chlorophenylacetate.
Ethyl α,β-diphenylglycidate.
α,β-Diphenylglyceramide.
α,β-Diphenylglycidic acid.
β-Diethylaminoethyl α,β-diphenylglycidate.
Ethyl α-chloropropionate.
Ethyl α-methyl-β-phenylglycidate.
α-methyl-β-phenylglycidic acid.
β-Diethylaminoethyl α-methyl-β-phenylglycidate.
Ethyl α-ethoxyacetate.
Diphenyl-(ethoxymethyl)-carbinol
Diphenylacetaldehyde.
Ethyl β,β-diphenylpropionimino ethyl ether hydrochloride.
Ethyl β,β-diphenyllactate.
Ethyl α-(β-diethylaminoethoxy)-β,β-diphenylpropionate.
β,β-Diphenyllactic acid.
β-Diethylaminoethyl β,β-diphenyllactate.

Ethyl Mandelate.- A solution of 72 g. (0.5 mole) of crude mandelic acid in 350 cc. of absolute ethanol, which contained 15 g. of hydrogen chloride, was refluxed for five and one-half hours. The alcohol was removed by distillation, the residual oil was treated with water, and extracted with ether. After the ether solution had been washed with dilute sodium bicarbonate

solution, and dried over anhydrous magnesium sulfate, the ether was removed. The residue was then distilled; yield, 56 g. (62.3%); b.p. 135-136° (14 mm.)(94).

Ethyl α-Chlorophenylacetate.- A stirred mixture of 56 g. (0.31 mole) of ethyl mandelate and 25.3 g. (0.32 mole) of pyridine was treated, dropwise, with 38 g. (0.32 mole) of thionyl chloride. The reaction temperature was maintained at 50-55° during the addition, and pyridine hydrochloride separated from the mixture to form a lower, liquid phase. After it had been stirred at 120° for two hours, the cooled reaction mixture was poured into cold water from which the insoluble oil was extracted with ether. The ether solution was washed with water, dried over anhydrous magnesium sulfate and the ether was removed. Distillation of the residue yielded the desired chloro ester; yield, 55.5 g. (90%); b.p. 125-126° (11 mm.)(95).

Ethyl α,β-Diphenylglycidate.- A solution of 15.9 g. (0.15 mole) of freshly distilled benzaldehyde and 29.8 g. (0.15 mole) of ethyl α-chlorophenylacetate in 75 cc. of anhydrous ether was cooled to 0-4° in an ice-salt bath. While the solution was stirred, there was added, in portions, 11.6 g. (0.17 mole) of sodium ethylate over a period of two hours. The mixture was allowed to remain for twelve hours at room temperature, after which the ether was removed by distillation. The viscous residue was heated on a steam-bath for one-half hour and cooled. It was then covered with ether, treated with a solution of 9 cc. of glacial acetic acid in 200 cc. of water,

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(94) Darapsky (J. prakt. Chem., (2) 96, 251 (298) (1917)) reported 141° (15 mm.).
(95) Darzens(76) reported 133° (12 mm.).

and stirred until two clear layers were obtained. The layers were separated, the aqueous layer was extracted with ether, and the ether solution was combined with the ether layer. The ether solution was washed with water and dilute sodium bicarbonate solution until the washings were slightly alkaline after which it was dried over anhydrous magnesium sulfate. The ether was removed, and the residual oil distilled; yield, 22.8 g. (56.6%); b.p. 161-163° (2 mm.). The oil solidified, and, after recrystallization from 95% ethanol, melted at 59-60°.

Anal. Calcd. for $C_{17}H_{16}O_3$: C, 76.10. H, 6.04.

Found: C, 75.83. H, 6.04.

An appreciable quantity of the corresponding acid was obtained from the bicarbonate wash solutions by acidification. The precipitated acid weighed 7.9 g. (21.8%) and melted at 121-122° (dec.)(96) after recrystallization from a mixture of ether and petroleum ether (60-70°).

In order to establish the identity of the acid, it was esterified with diazomethane in ether solution; the methyl ester melted 71-72° after recrystallization from methanol. When the melted ester was allowed to solidify, and then remelted, the melting point was 79-80°(97). The lower melting point was not, however, raised by recrystallization from solvents other than methanol.

Amidification of Ethyl α,β-Diphenylglycidate.- A mixture of 1.0 g. (0.0037 mole) of ethyl α,β-diphenylglycidate, 15 cc. of ethanol and 5 cc. of 28% aqueous ammonia was allowed to

(96) Kohler and Brown(50) reported the melting point of one form of this acid as 121°.

(97) Kohler and Brown(50) found 80° for one form of the ester.

remain at room temperature for twenty-four hours. The clear solution was evaporated to dryness, and the solid residue was recrystallized from ethanol. There was obtained 0.3 g. (32%) of α,β-diphenylglyceramide, m.p. 133-134°[98].

Anal. Calcd. for $C_{15}H_{15}NO_3$: N, 5.45.

Found: N, 5.65.

α,β-Diphenylglycidic Acid.- Ten and seven-tenths grams (0.04 mole) of ethyl α,β-diphenylglycidate were dissolved in a cold solution of sodium ethylate, prepared from 0.9 g. (0.04 g. atom) of sodium and 80 cc. of absolute ethanol. The solution was then treated with 0.7 cc. (0.04 mole) of water, and allowed to remain at about 8° for seven hours. The precipitated sodium salt of the acid was collected on a filter, washed with cold ethanol and dried; yield, 9.7 g. (92.4%). Acidification of an aqueous solution of this salt precipitated 0.85 g. (93.8%) of the corresponding acid which, after recrystallization from a mixture of ether and petroleum ether (60-70°), melted at 121-122° (dec.).

Anal. Calcd. for $C_{15}H_{12}O_3$: Neut. Equiv., 240.3.

Found: Neut. Equiv., 242.2.

β-Diethylaminoethyl α,β-Diphenylglycidate Hydrochloride.- A solution, which contained 2.4 g. (0.01 mole) of α,β-diphenylglycidic acid and 1.4 g. (0.01 mole) of β-diethylaminoethyl chloride in 35 cc. of chloroform, was refluxed for thirteen hours. The hot solution was filtered, and the filtrate was evaporated to an oil which readily solidified. The

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(98) Kohler and Brown[50] reported 135°.

solid ester was recrystallized twice from a mixture of chloroform and ether; yield, 3.1 g. (82.4%); m.p. 154-155°.

Anal. Calcd. for $C_{21}H_{26}ClNO_3$: N, 3.73. Cl^-, 9.43.

Found: N, 3.67. Cl^-, 9.40

Ethyl α-Chloropropionate.- A mixture of 53 g. (0.45 mole) of ethyl lactate and 40 g. (0.5 mole) of pyridine was stirred and maintained at room temperature while 60 g. (0.5 mole) of thionyl chloride was added, dropwise, over a period of forty minutes. During the addition the mixture became quite thick because of the separation of the pyridine hydrochloride which was formed. The stirred mixture was then heated in an oil-bath at 110-120° for two hours after which it was cooled, and poured into water. The insoluble oil was extracted with ether, the ether solution was washed with water, and dried over anhydrous magnesium sulfate. After the ether was removed, the residue was distilled; yield, 48.5 g. (79%); b.p. 138-140°[99].

Ethyl α-Methyl-β-phenylglycidate.- A mixture of 26.6 g. (0.25 mole) of freshly distilled benzaldehyde, 34.2 g. (0.25 mole) of ethyl α-chloropropionate, and 100 cc. of anhydrous ether was cooled to 0°. Pulverized sodamide (10 g.; 0.25 mole) was added to the stirred mixture over a period of one hour; the reaction temperature was maintained at 0-10° during this time. The reaction mixture was stirred at room temperature for five hours, and was then poured into a mixture of 15 cc. of glacial acetic acid and 250 cc. of water. The layers were separated,

(99) Darzens[76] reported 144-145°.

the ether layer was washed with water and dilute sodium bicarbonate solution until the washings were alkaline, and dried over anhydrous magnesium sulfate. The ether was removed, and the residue was distilled; yield, 20 g. (38.8%); b.p. 117-121° (4 mm.)(100).

α-Methyl-β-phenylglycidic Acid.- Fifteen and four-tenths grams (0.075 mole) of ethyl α-methyl-β-phenylglycidate were dissolved in a cold, alcoholic solution of sodium ethylate, prepared from 1.75 g. (0.075 g. atom) of sodium and 50 cc. of absolute ethanol. Water (1.35 cc.; 0.075 mole) was then added, and the solution was allowed to remain at about 8° for two hours, whereupon the sodium salt of the acid separated. The salt was collected on a filter, washed with cold ethanol and dried; yield, 13.6 g. (90.7%). In order to obtain the free acid, 8.0 g. (0.04 mole) of the salt were dissolved in water, the solution was covered with ether and acidified with hydrochloric acid. The ether layer was separated, dried over anhydrous magnesium sulfate, and evaporated to an oil under reduced pressure. The residual oil solidified and was recrystallized from petroleum ether (60-70°); yield, 6.0 g. (80%); m.p. 68-69°.

Anal. Calcd. for $C_{10}H_{10}O_3$: Neut. Equiv., 178.2.

Found: Neut. Equiv., 178.8.

As a further check on its identity, 0.5 g. of the acid was heated at 150-160° until gas evolution ceased (one hour).

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(100) Darzens[51] found 153-154° (18 mm.); Richard[52] reported 145.5° (18 mm.).

The residual oil was identified as phenylacetone by means of its semicarbazone, m.p. 186-187.5°*.

β-Diethylaminoethyl α-Methyl-β-phenylglycidate Hydrochloride.- A solution of 2.3 g. (0.011 mole) of α-methyl-β-phenylglycidic acid and 1.5 g. (0.011 mole) of β-diethylaminoethyl chloride in 30 cc. of chloroform was refluxed for thirteen hours. After the mixture had been filtered, the solvent was removed by vacuum distillation, and the residual oil was triturated under ether until it solidified. The solid was isolated by filtration, washed with ether and dried. The crude ester hydrochloride weighed 3.0 g. (86%), and was recrystallized from a mixture of ethanol and ether; m.p. 115-116°.

Anal. Calcd. for $C_{16}H_{24}ClNO_3$: N, 4.46. Cl^-, 11.30.

Found: N, 4.36. Cl^-, 11.39.

Ethyl α-Ethoxyacetate.- A solution of 123 g. (1.0 mole) of ethyl chloroacetate in 100 cc. of absolute ethanol was added, dropwise, to a stirred solution of 23 g. (1.0 g. atom) of sodium in 400 cc. of absolute ethanol over a period of one hour. The reaction temperature was maintained at 25-35° during the addition. After the reaction mixture had been stirred for an additional one-half hour at this temperature, it was refluxed for thirty minutes. Approximately half of the solvent was removed, and the precipitated sodium chloride

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* Several different values for the melting point of this substance are reported (Beilstein, Vol. VII, p. 304). However, there was no depression in the melting point of our semicarbazone when it was mixed with a sample prepared from authentic phenylacetone.

was removed by filtration. Distillation of the filtrate yielded 77.5 g. (58.5%) of ethyl ethoxyacetate, b.p. 148-151°[101].

Diphenyl-(ethoxymethyl)-carbinol.- To a stirred solution of phenylmagnesium bromide, prepared from 18.0 g. (0.74 mole) of magnesium, 118.0 g. (0.75 mole) of bromobenzene and 350 cc. of anhydrous ether, there was added a solution of 45.0 g. (0.34 mole) of ethyl ethoxyacetate in 100 cc. of anhydrous ether over a period of one hour. During the addition, the reaction temperature was controlled so that gentle reflux of the solvent was maintained. After the reaction mixture had been stirred at room temperature for two hours, it was poured into a mixture of ice and water to which 70 cc. of glacial acetic acid had been added. The layers were separated, the aqueous layer was extracted with ether, and the ether solutions were combined. The ether solution was washed with water, and dilute sodium bicarbonate solution after which it was dried over anhydrous magnesium sulfate. The ether was removed, and the residue was distilled; yield, 62.0 g. (75%); b.p. 165-168° (6-7 mm.)[102].

Diphenylacetaldehyde.- (Method A) A stirred mixture of 79.0 g. (0.33 mole) of diphenyl-(ethoxymethyl)-carbinol, and 83.0 g. (0.66 mole) of oxalic acid dihydrate was heated, by means of an oil-bath, at 120° for three hours. When the mixture had cooled, the lower oxalic acid layer solidified, and the upper oily layer was decanted. The residual oxalic acid, to

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(101) Daniloff and Venus-Danilova[54] reported 71-72° (34 mm.).
(102) Daniloff and Venus-Danilova[54] found 189-191° (20 mm.).

which an appreciable amount of oil had adhered, was dissolved in water, and the oil was extracted with ether. The decanted oil was added to the ether solution, and the solution was washed with dilute sodium bicarbonate solution before it was dried over anhydrous magnesium sulfate. The solvent was removed and the residue was distilled: yield, 52 g. (81.3%); b.p. 150-153° (6-7 mm.)[103]. Its identity was confirmed by its semicarbazone, m.p. 158-159°[87].

(Method B) Three and nine-tenths grams of β,β-diphenylglycidic acid were heated at 100-110° until the evolution of carbon dioxide had ceased (15 minutes). Distillation of the oily residue yielded 2.4 g. (75.5%) of diphenylacetaldehyde, b.p. 170-174° (16 mm.). Its semicarbazone melted at 159-160°[87].

Ethyl β,β-Diphenylpropionimino Ethyl Ether Hydrochloride.- A solution of 9.8 g. (0.05 mole) of diphenylacetaldehyde in 70 cc. of ether was added to a solution of 4.2 g. (0.085 mole) of sodium cyanide, contained in a separatory funnel. The mixture was cooled and treated, dropwise, with 14.5 cc. (0.085 mole) of 18% hydrochloric acid over a period of forty-five minutes. The mixture was shaken frequently during this time. The ether layer was then washed successively with dilute bicarbonate solution, dilute sodium bisulfite solution and water, after which it was dried over anhydrous magnesium sulfate. The dry ether solution, which contained β,β-diphenyllactonitrile*,

(103) Daniloff and Venus-Danilova[54] reported the boiling point as 193-195° (33 mm.).

* An attempted hydrolysis of this hydroxy nitrile to β,β-diphenyllactic acid was unsuccessful.

was treated directly with 2.6 cc. (0.045 mole) of absolute ethanol and 3.5 g. (0.096 mole) of hydrogen chloride. After the solution had remained at room temperature for one week, the precipitated solid was isolated by filtration, washed with ether and dried; yield, 4.2 g. (27.4%); m.p. 135-136° (dec.)(104).

Ethyl β,β-Diphenyllactate.- (Method A) Three and nine-tenths grams (0.013 mole) of ethyl β,β-diphenylglycidimino ethyl ether hydrochloride were stirred into 75 cc. of water at room temperature. As the salt dissolved, and was hydrolyzed, the ester separated simultaneously as an oil which readily crystallized. The solid ester was isolated by filtration, washed and dried; yield, 3.3 g. (96%); m.p. 65-66°(105).

(Method B) A solution of 16 g. (0.06 mole) of ethyl diphenylpyruvate in 80 cc. of absolute ethanol was hydrogenated at an initial pressure of 48 lbs. at 25° over Raney nickel catalyst. It was necessary to add fresh catalyst after six and one-half hours, and the reduction was completed after fourteen hours. The catalyst was removed by filtration, and the filtrate was concentrated to an oil which readily solidified. The ester weighed 16.0 g. (100%) and melted at 66-67° after recrystallization from petroleum ether (60-70°).

(Method C) Two and seven-tenths grams (0.01 mole) of ethyl β,β-diphenylglycidate, dissolved in 40 cc. of absolute ethanol, was hydrogenated at room temperature over Raney nickel

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(104) Weise(58) reported 135° (dec.).
(105) Weise(58) reported 66°.

catalyst. The reduction was completed in one hour. The oily residue, which remained after the catalyst and solvent were removed, solidified; yield, 2.6 g. (96%); m.p. 65-66° after recrystallization from petroleum ether (60-70°).

Ethyl α-(β-Diethylaminoethoxy)-β,β-diphenyl-propionate Hydrochloride.- A mixture of 6.9 g. (0.026 mole) of ethyl β,β-diphenyllactate, 0.6 g. (0.026 g. atom) of powdered sodium, and 75 cc. of anhydrous ether was refluxed until nearly all of the sodium had reacted (7 hours). Four and one-half grams (0.033 mole) of β-diethylaminoethyl chloride were added, and the mixture was refluxed for an additional four hours. The solution was diluted with 40 cc. of toluene, distilled until the liquid temperature reached 100°, and refluxed for five hours. The cooled mixture was then extracted with dilute hydrochloric acid, and the acidic aqueous solution, after clarification by an ether extraction, was made strongly alkaline. The liberated oil was extracted with ether, the ether solution was dried over anhydrous magnesium sulfate, and the ether was removed. Distillation of the residue yielded 6.1 g. (63.5%) of the desired ester, b.p. 160-162° (0.01 mm.).

The hydrochloride of the above ester, prepared from an ether solution of the base and ethereal hydrogen chloride, melted at 144-147° after recrystallization from a mixture of ethanol and ether.

Anal. Calcd. for $C_{23}H_{32}ClNO_3$: N, 3.45. Cl^-, 8.73.

Found: N, 3.56. Cl^-, 8.88

β,β-Diphenyllactic Acid.- (Method A) A mixture of 3.3 g. (0.012 mole) of ethyl β,β-diphenyllactate, 14 g. (0.024 mole) of potassium hydroxide and 35 cc. of methanol was refluxed for four hours. The solvent was removed, the residual oil was dissolved in water, and the solution was acidified. The organic acid separated as an oil but soon solidified, and was isolated by filtration; yield, 2.7 g. (95%); m.p. 158-159°(106) after recrystallization from water.

(Method B) A solution of 1.2 g. (0.005 mole) of diphenylpyruvic acid in 50 cc. of ethanol was hydrogenated at room temperature under an initial pressure of 39 lbs. The catalyst was palladium on charcoal, and the reduction was completed in four hours. The solid residue, which remained after the removal of the catalyst and solvent, weighed 1.1 g. (91%) and melted at 158-159°.

(Method C) A solution of 5.4 g. (0.02 mole) of ethyl β,β-diphenylglycidate in 75 cc. of absolute ethanol was refluxed, and 4.0 g. (0.16 g. atom) of sodium were added, in small pieces, over a period of one-half hour. The alcohol was removed, the residue was treated with water, and the solution was acidified. The oil which separated was stirred with aqueous sodium carbonate solution, and the insoluble portion was extracted with ether. Acidification of the aqueous solution precipitated a solid which was isolated by filtration; yield, 1.3 g. (27%) of β,β-diphenyllactic acid, m.p. 153-155°. Evaporation of the

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(106) Weise(58) reported 159°.

ether solution yielded 2.0 g. of an oil which was not identified.

β-Diethylaminoethyl β,β-Diphenyllactate Hydrochloride.- To a solution of 2.7 g. (0.011 mole) of β,β-diphenyllactic acid in 40 cc. of isopropyl alcohol there was added a dry ether solution of β-diethylaminoethyl chloride which had been obtained from 3.4 g. (0.02 mole) of the corresponding hydrochloride. The solution was distilled until the ether had been removed, and the residual alcoholic solution was refluxed for twelve hours. The hot solution was filtered, and the filtrate was evaporated to an oil which solidified when triturated under anhydrous ether. After recrystallization from a mixture of ethanol and ether, there was obtained 3.0 g. (72%) of the ester hydrochloride, m.p. 141-142°.

Anal. Calcd. for $C_{21}H_{28}ClNO_3$: N, 3.71. Cl^-, 9.38.
Found: N, 3.47. Cl^-, 9.48.

Preparation of the following compounds:

α-Methyl-β,β-diphenyllactic acid.
Ethyl α-methyl-β,β-diphenyllactate.
β-Diethylaminoethyl α-methyl-β,β-diphenyllactate.
α,β,β-Triphenyllactic acid.
β-Diethylaminoethyl α,β,β-triphenyllactate.
α,β,β-Triphenylacrylic acid.
β-Diethylaminoethyl α,β,β-triphenylacrylate.

α-Methyl-β,β-diphenyllactic Acid.- A solution of methylmagnesium iodide, prepared from 2.8 g. (0.11 mole) of magnesium, 15.6 g. (0.11 mole) of methyl iodide and 100 cc. of anhydrous ether, was added, dropwise, to a stirred solution of 9.6 g. (0.04 mole) of diphenylpyruvic acid in 140 cc. of anhydrous

ether. The pyruvic acid was added over a period of one hour, and during this time the temperature of the reaction mixture was maintained at 10-15°. After the mixture had been stirred for an additional hour at room temperature, it was decomposed by the slow addition of 20 cc. of concentrated hydrochloric acid diluted with 80 cc. of water. The layers were separated, the ether layer was washed with water, and dried over anhydrous magnesium sulfate. The solid residue which remained after the removal of the ether weighed 8.0 g. (83.2%) and melted at 167-168.5° after recrystallization from a mixture of chloroform and petroleum ether (60-70°)(107).

Ethyl α-Methyl-β,β-diphenyllactate.- A solution of 1.0 g. of α-methyl-β,β-diphenyllactic acid in 40 cc. of absolute ethanol, which contained 3.0 g. of hydrogen chloride, was refluxed for four hours. The solvent was removed, and the residual oil was dissolved in ether. After the solution had been washed with dilute sodium bicarbonate and water, it was dried over anhydrous magnesium sulfate. The ether was removed, and the residue was recrystallized from a small volume of absolute ethanol; yield 0.5 g. (47%); m.p. 73-74°(108).

The corresponding methyl ester, prepared in 69% yield by essentially the same method, melted at 88-89° after recrystallization from methanol(109).

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(107) Bardon and Ramart(44) reported 167° for an acid believed by them to be β-methyl-β,β-diphenyllactic acid.
(108) Bardon and Ramart(44) reported 73° for an ester believed by them to be ethyl β-methyl-β,β-diphenyllactate.
(109) Kohler and Weiner(67) found 87-88°.

β-Diethylaminoethyl α-Methyl-β,β-diphenyllactate Hydrochloride.- A mixture of 3.85 g. (0.015 mole) of α-methyl-β,β-diphenyllactic acid, 2.05 g. (0.015 mole) of β-diethylaminoethyl chloride and 40 cc. of isopropanol was refluxed for five hours, after which the solvent was removed in an air-stream. The residual oil solidified when triturated under anhydrous ether and the solid was recrystallized from a mixture of ethanol and ether. The ester hydrochloride melted at 140-141°, and weighed 4.5 g. (58.6%).

Anal. Calcd. for $C_{22}H_{30}ClNO_3$: N, 3.57. Cl^-, 9.05.

Found: N, 3.68. Cl^-, 9.14.

α,β,β-Triphenyllactic Acid.- A solution of phenylmagnesium bromide, prepared from 2.4 g. (0.1 mole) of magnesium, 15.7 g. (0.1 mole) of bromobenzene and 115 cc. of anhydrous ether, was added, dropwise, to a stirred solution of 9.6 g. (0.04 mole) of diphenylpyruvic acid in 160 cc. of anhydrous ether. The reaction temperature was maintained at 10-15° during the addition period of forty-five minutes. After the mixture had been stirred at approximately 20° for four hours, it was filtered. The solid complex was stirred into a mixture of 20 cc. of concentrated hydrochloric acid and 700 cc. of water, and the organic acid was isolated by filtration. The crude acid weighed 9.9 g. (78%), and melted at 235-236° (dec.)(110) after recrystallization from a mixture of acetone and petroleum ether (60-70°).

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(110) Kohler and Weiner[67] found the melting point to be 243-245° (dec.).

The methyl ester of the acid, prepared in 56% yield by direct esterification, melted at 183-184° after recrystallization from ethanol(111).

β-Diethylaminoethyl α,β,β-Triphenyllactate Hydrochloride.- One and four-tenths grams (0.01 mole) of β-diethylaminoethyl chloride were added to a suspension of 3.2 g. (0.01 mole) of α,β,β-triphenyllactic acid, and the mixture was refluxed for five hours. After the solution had been filtered and concentrated somewhat, it was cooled whereupon the product separated as a solid; yield, 2.7 g. (60%); m.p. 193-194° after recrystallization from ethanol.

Anal. Calcd. for $C_{27}H_{32}ClNO_3$: N, 3.09. Cl^-, 7.81.

Found: N, 3.11. Cl^-, 8.01.

α,β,β-Triphenylacrylic Acid.- Three and two-tenths grams (0.01 mole) of α,β,β-triphenyllactic acid were heated, by means of a metal-bath, at 245° for fifteen minutes. Brisk gas evolution was noted during this time. The cooled residue was treated with warm, dilute sodium hydroxide solution whereupon most of the material dissolved. After the mixture had been filtered, the alkaline solution was boiled with decolorizing charcoal, filtered, and the filtrate was acidified. The precipitated acid was collected on a filter, washed and dried; yield, 1.5 g. (50%); m.p. 209-213°(112).

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(111) Kohler and Weiner(67) found 186°; Wegmann and Dahn(68) reported 174-175°.

(112) Kohler and Weiner(67) reported 208-212°.

β-Diethylaminoethyl α,β,β-Triphenylacrylate Hydrochloride.- A solution of 1.5 g. (0.005 mole) of α,β,β-triphenylacrylic acid and 0.7 g. (0.005 mole) of β-diethylaminoethyl chloride in 35 cc. of isopropyl alcohol was refluxed for seven hours. The solid residue, which remained after the removal of the solvent, was recrystallized from a mixture of isopropanol and ether. The yield of pure ester hydrochloride was 1.5 g. (69%); m.p. 201-202°.

Anal. Calcd. for $C_{27}H_{30}ClNO_2$: N, 3.21. Cl^-, 8.13.
Found: N, 3.39. Cl^-, 8.25.

Preparation of the following compounds:

Diphenylacetamide.
N-(β-Diethylaminoethyl)-diphenylacetamide.
Ethyl β,β-diphenyl-β-hydroxypropionate.
β,β-Diphenyl-β-hydroxypropionic acid.
Ethyl β,β-diphenylacrylate.
β,β-Diphenylacrylic acid.
β-Diethylaminoethyl β,β-diphenylacrylate.
β-Diethylaminoethyl α-bromo-β,β-diphenylacrylate.

Diphenylacetamide.- Diphenylacetyl chloride, prepared in 96.5% yield by a known procedure[113], was reacted with ammonia to form this compound; yield, 85.7%; m.p. 167-168°[114].

N-(β-Diethylaminoethyl)-diphenylacetamide.- To 8.5 g. (0.04 mole) of diphenylacetamide, suspended in 125 cc. of dry toluene, there was added 1.7 g. (0.044 mole) of powdered sodamide, and the suspension was stirred and refluxed for three hours.

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(113) Staudinger, Ber., 44, 1619 (1911).
(114) Japp and Knox, (J. Chem. Soc., 87, 681 (1905)) found 168°.

During this time, ammonia was evolved as the amide reacted with the sodamide to form the sodium salt which immediately separated from the mixture. The cooled mixture was then treated with an ether solution of β-diethylaminoethyl chloride, obtained in the usual manner from 12 g. (0.07 mole) of β-diethylaminoethyl chloride hydrochloride, and allowed to remain for twelve hours at room temperature. After the reaction mixture had been stirred and refluxed for two hours, the ether was removed by distillation, and the toluene solution was stirred and refluxed for an additional ten hours. The cooled reaction mixture was then treated with 10 cc. of ethanol to destroy any unreacted sodamide, and the solvent was removed by vacuum distillation. The solid residue was stirred in a mixture of 8 cc. of concentrated hydrochloric acid and 150 cc. of water for one-half hour, after which the undissolved solid was removed by filtration. This solid (1 g.) was unreacted diphenylacetamide. Alkalization of the acidic filtrate precipitated a solid which was collected on a filter, washed with water, and dried. After recrystallization from a mixture of chloroform and petroleum ether (60-70°), there was obtained 6.6 g. (53.1%; 59.8% based on the amount of diphenylacetamide actually consumed) of the amide base; m.p. 93-94°[115].

Anal. Calcd. for $C_{20}H_{26}N_2O$: N, 8.82.

Found: N, 9.00.

In order to prepare the hydrochloride of the above amide, an ethanolic solution of the amide (1.5 g.) was treated with

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(115) Meischer, Meisel and Hoffmann[78] reported 94°.

excess ethereal hydrogen chloride, and then diluted with anhydrous ether. The solid amide hydrochloride, which separated, was collected on a filter, washed and dried; yield, 1.5 g. (89.3%); m.p. 145-146°(116).

The methobromide was prepared in the following manner: A mixture of 3.0 g. (0.01 mole) of the amide, 5.0 g. (0.05 mole) of methyl bromide, and 50 cc. of chloroform, contained in a stoppered citrate bottle, was allowed to remain at room temperature for eighteen hours. It was then heated on a steam-bath for one-half hour, after which the solvent was removed. The residual oil solidified when triturated under anhydrous ether, and the solid was recrystallized from a mixture of ethanol and ether. The quaternary compound weighed 2.9 g. (71.5%), and melted at 120-122°.

Anal. Calcd. for $C_{21}H_{29}BrN_2O$: N, 6.91 Br^-, 19.72.
Found: N, 6.89 Br^-, 19.90.

Ethyl β,β-Diphenyl-β-hydroxypropionate.- To 7.5 g. of clean, granular zinc, whose surface had been etched with iodine vapor, there was added 20 cc. of a solution of 18.2 g. (0.1 mole) of benzophenone and 18.5 g. (0.11 mole) of ethyl bromoacetate in 80 cc. of dry benzene. The mixture was stirred and warmed to initiate the reaction after which the remainder of the benzene solution was added over a period of fifteen minutes. After the reaction mixture had been stirred and refluxed for an additional forty-five minutes, it was cooled, and poured into 110 cc. of 10% aqueous sulfuric acid. The layers

(116) Burtner and Cusic(56) reported 145°.

were separated, the aqueous layer was thoroughly extracted with ether, and the extracts were combined with the benzene layer. The solution was washed successively with dilute sulfuric acid and water, and the solvent was removed by vacuum distillation. The residual oil solidified, and was recrystallized from isopropyl alcohol. The pure ester weighed 25 g. (92.5%), and melted at 85-87°(117).

β,β-Diphenyl-β-hydroxypropionic Acid.- A solution, which contained 92.5 g. (0.34 mole) of the above ester, and 40 g. (0.71 mole) of potassium hydroxide in 300 cc. of methanol, was refluxed for twenty-six hours. The residue, which remained after the removal of the solvent, was treated with 800 cc. of water, and the solution was extracted with ether to remove a small amount of insoluble material. Acidification of the aqueous solution precipitated the desired acid, which was collected on a filter, washed with water and dried; yield, 70 g. (85%); m.p. 215-216° (dec.)(118).

Ethyl β,β-Diphenylacrylate.- Fifty grams of ethyl β,β-diphenyl-β-hydroxypropionate were heated on a steam-bath for three hours while a slow stream of hydrogen chloride was bubbled through the molten ester. The water, which had formed, was separated from the oil, and the oil was distilled. There was obtained 45 g. (96%) of the acrylic ester, b.p. 152-155° (1-2 mm.)(119).

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(117) Rupe and Busolt(60) reported 87°.
(118) Rupe and Busolt(60) found 212°. Their yield was 70%.
(119) Schlenk and Bergmann(63) reported 207° (17 mm.)

β,β-Diphenyacrylic Acid.- (Method A) A mixture of 45 g. (0.18 mole) of ethyl β,β-diphenylacrylate, 22.4 g. (0.4 mole) of potassium hydroxide and 300 cc. of methanol was refluxed for twelve hours after which the solvent was removed by vacuum distillation. The residue was dissolved in 300 cc. of water, the solution was filtered, and acidified. The precipitated organic acid was filtered, washed and dried; yield, 38 g. (95%); m.p. 157-158°(120).

(Method B) Several attempts were made to dehydrate β,β-diphenyl-β-hydroxypropionic acid by means of acetic anhydride, hydrogen chloride, phosphorous pentoxide, or heat alone. The best yield was obtained with phosphorous pentoxide in the following manner: A mixture of 4.8 g. (0.02 mole) of the hydroxy acid, 5 g. of Super-cel, and 120 cc. of dry benzene was stirred vigorously at 40°, and treated with 5 g. of phosphorous pentoxide. After the green mixture had been stirred and refluxed for one-half hour, it was filtered, and the filtrate was evaporated to dryness. The semi-solid residue was dissolved in aqueous sodium carbonate solution, treated with Norite, filtered, and the filtrate was acidified. The precipitated acid was collected on a filter, washed and dried; yield, 2.0 g. (44.5%); m.p. 156-158°.

β-Diethylaminoethyl β,β-Diphenylacrylate Hydrochloride.- A dry ether solution of β-diethylaminoethyl chloride, which had been obtained from 38 g. (0.22 mole) of the corresponding

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(120) Kohler and Johnstin(59) found 155°; Rupe and Busolt(60) reported 162°.

hydrochloride salt, was added to a solution of 33.6 g. (0.15 mole) of β,β-diphenylacrylic acid in 200 cc. of isopropyl alcohol. The solution was then distilled to remove the ether, and the residual alcoholic solution was refluxed for eleven hours. The solution was filtered, and evaporated to an oil which solidified when it was triturated under anhydrous ether. The ester hydrochloride weighed 43 g. (80%), and melted at 157-159° after recrystallization from acetone[121].

β-Diethylaminoethyl α-Bromo-β,β-diphenylacrylate.- A solution of 12.5 g. (0.035 mole) of β-diethylaminoethyl β,β-diphenylacrylate hydrochloride in 70 cc. of chloroform was treated with 5.6 g. (0.035 mole) of bromine and allowed to remain at room temperature for twenty-seven hours. The dark red oil, which remained after the removal of the solvent, was covered with ether, treated with a solution of 1 g. of sodium bisulfite in 200 cc. of water, and the mixture was stirred until two clear layers were obtained. The mixture was then made alkaline with sodium hydroxide, and the ether layer, which contained the ester base, was washed with water. After the ether solution had been dried over anhydrous magnesium sulfate, it was evaporated, and the residual oil was distilled; yield, 11.0 g. (78%); b.p. 172-176° (0.01 mm.)

The hydrochloride salt was prepared by the addition of a slight excess of ethereal hydrogen chloride to an ether solution of the base; m.p. 155-156° after recrystallization from a mixture of ethanol and ether.

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(121) Burtner and Cusic[56] reported 159-160°.

Anal. Calcd. for $C_{21}H_{26}BrClNO_2$: N, 3.19 Cl^-, 8.08.

Found: N, 3.07 Cl^-, 7.99.

The methobromide of this ester was prepared as follows: 2.5 g. (0.006 mole) of the ester base was dissolved in 50 cc. of ethanol which contained 0.68 g. (0.007 mole) of methyl bromide. The solution, contained in a stoppered citrate bottle, was heated on a steam-bath for four hours. The solvent was removed, and the residue was triturated under anhydrous ether whereupon it became solid. After recrystallization from a mixture of isopropyl alcohol and ether, the quaternary compound melted at 90.5-92°; yield, 1.7 g. (55%).

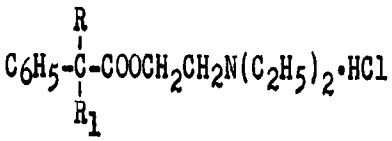
Anal. Calcd. for $C_{22}H_{27}Br_2NO_2$: N, 2.82. Br^-, 16.07.

Found: N, 2.75. Br^-, 16.08.

The compounds, which we have prepared for pharmacological testing, are listed in the following tables.

TABLE II

β-Diethylaminoethyl Esters of Substituted Phenylacetic Acids

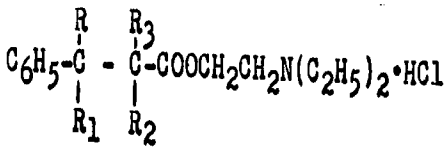


Code No.	R	R1	Formula	M.p., °C.	Nitrogen, % Calcd.	Nitrogen, % Found	Halogen, % Calcd.	Halogen, % Found
JF-714	Br	H	$C_{14}H_{21}Br_2NO_2$ (a)	105-107	3.55	3.58	40.45	40.88
JF-715	Cl	H	$C_{14}H_{21}Cl_2NO_2$	126-128	4.57	4.49	11.58	11.78
JF-713	Br	C_6H_5	$C_{20}H_{25}Br_2NO_2$ (a)	164-165	2.97	3.12	33.92	34.20
JF-706	Cl	C_6H_5	$C_{20}H_{25}Cl_2NO_2$ (b)	152.5-153.5	---	---	---	---
JF-721	OC_2H_5	C_6H_5	$C_{22}H_{30}BrNO_3$	150-151	3.21	3.15	18.32	18.28
JF-731	$N(CH_3)_2$	C_6H_5	$C_{22}H_{31}ClN_2O_2$	182-183(dec.)	7.17	7.09	9.08	9.15
JF-742	$N(CH_3)_2$	C_6H_5	$C_{23}H_{33}BrN_2O_2$ (c)	190-192(dec.)	6.24	6.28	17.78	17.53
JF-732	$N(CH_3)_2$	H	$C_{16}H_{28}Cl_2N_2O_2$	194-195(dec.)	7.98	7.98	20.18	20.29
JF-734	NC_5H_{10} (d)	H	$C_{19}H_{32}Cl_2N_2O_2$	194-195	7.16	7.20	18.12	18.18
JF-737	NC_4H_8O (e)	H	$C_{18}H_{30}Cl_2N_2O_3$	170-171	7.12	7.25	18.03	17.77
JF-738	NC_4H_8O	H	$C_{19}H_{31}BrN_2O_3$ (c)	144-146	6.75	6.84	19.24	19.39

(a) Hydrobromide.
(b) Previously prepared by Burtner and Cusic[56].
(c) Methobromide.
(d) NC_5H_{10} = Piperidino.
(e) NC_4H_8O = Morpholino.

TABLE III

β-Diethylaminoethyl Esters of Substituted β-Phenylpropionic Acids



Code No.	R	R_1	R_2	R_3	Formula	M.p., °C.	Nitrogen, % Calcd.	Nitrogen, % Found	Halogen, % Calcd.	Halogen, % Found
JF-707	C_6H_5	H	OH	H	$C_{21}H_{28}ClNO_3$	141-142	3.71	3.47	9.38	9.48
JF-709	C_6H_5	OH	OH	H	$C_{21}H_{28}ClNO_4$	194-195(dec.)	3.56	3.47	9.02	8.94
JF-710	C_6H_5			H	$C_{21}H_{26}ClNO_3$	155-156	3.73	3.71	9.43	9.59
JF-717	C_6H_5	H	C_6H_5	OH	$C_{27}H_{32}ClNO_3$	193-194	3.09	3.11	7.81	8.01
JF-718	C_6H_5	H	CH_3	OH	$C_{22}H_{30}ClNO_3$	140-141	3.57	3.68	9.05	9.14
JF-722	H			C_6H_5	$C_{21}H_{26}ClNO_3$	154-155	3.73	3.67	9.43	9.40
JF-723	H			CH_3	$C_{16}H_{24}ClNO_3$	115-116	4.46	4.36	11.30	11.39
JF-708	C_6H_5	OH	H	H	$C_{21}H_{28}ClNO_3$(a)	148-150	----	----	----	----

(a) Previously prepared by Blicke and Kaplan[2].

TABLE IV

β-Diethylaminoethyl Esters of Substituted Acrylic Acids

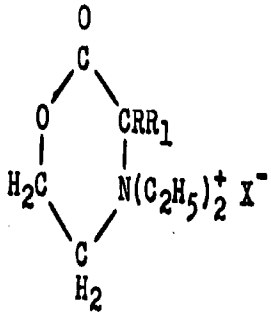
$(C_6H_5)_2C=C(R)COOCH_2CH_2N(C_2H_5)_2 \cdot HCl$

Code No.	R	Formula	M.p., °C.	Nitrogen, % Calcd.	Nitrogen, % Found	Halogen, % Calcd.	Halogen, % Found
JF-704	H	$C_{21}H_{26}ClNO_2$ (a)	160-161	---	---	---	---
JF-705	Br	$C_{21}H_{25}BrClNO_2$	155-156	3.19	3.07	8.08 (b)	7.99
JF-733	Br	$C_{22}H_{27}Br_2NO_2$ (c)	90.5-92	2.82	2.75	16.07 (b)	16.08
JF-720	C_6H_5	$C_{27}H_{30}ClNO_2$	201-202	3.21	3.39	8.13	8.25

(a) Previously prepared by Burtner and Cusic[56].
(b) Ionic halogen.
(c) Methobromide.

TABLE V

Substituted 2-Morpholones



Code No.	R	R_1	X	Formula	M.p., °C.	Nitrogen, % Calcd.	Nitrogen, % Found	Halogen, % Calcd.	Halogen, % Found
JF-711	H	H	Cl	$C_8H_{16}ClNO_2$	198-199(dec.)	----	----	18.31	18.39
JF-716	H	C_6H_5	Br	$C_{14}H_{20}BrNO_2$	191-192(dec.)	4.46	4.55	25.43	25.18
JF-743	C_6H_5	C_6H_5	Cl	$C_{20}H_{24}ClNO_2$	177-179(dec.)	4.05	4.14	10.25	10.44

TABLE VI

Miscellaneous Compounds

Code No.	Formula	M.p., °C.	Nitrogen, % Calcd.	Nitrogen, % Found	Halogen, % Calcd.	Halogen, % Found
JF-735	$(C_6H_5)_2CHCONHCH_2CH_2N(C_2H_5)_2 \cdot HCl$ [a]	145-146	8.08	8.19	10.22	10.31
JF-736	$(C_6H_5)_2CHCONHCH_2CH_2N(C_2H_5)_2 \cdot CH_3Br$	120-122	6.91	6.89	19.72	19.90
JF-724	$(C_6H_5)_2CHCHCOOC_2H_5$ $\quad\quad\quad

PHARMACOLOGICAL DATA

The preliminary antispasmodic tests on our compounds were carried out under the direction of Dr. A. M. Lands of the Sterling-Winthrop Research Institute.

Initial tests of compounds of possible value as antispasmodic agents are always determined by the use of the Magnus method. In this procedure, a spastic condition is simulated in an isolated strip of rabbit intestine by immersion of the strip in a bath, which contains acetyl choline. The extent to which a given substance can counter-act the spasm (contraction) of the muscle is measured by means of a kymograph. In these tests, atropine is usually used as the standard for comparison; this alkaloid has been found to be effective, in a counter-action of spasm, in a dilution of 1:50,000,000 to 1:75,000,000.

It can be seen from the following table that only two compounds in our series, JF 713 and JF 706, are strong antispasmodics. Unfortunately, the data shown in the table represents pharmacological data on only about half of the compounds which were submitted for pharmacological evaluation.

TABLE VII

Antispasmodic Activity

Code No.	Formula	Spasmolytic Dose Dilution (Millions)
JF-704	$(C_6H_5)_2C{=}CHCOOCH_2CH_2N(C_2H_5)_2{\cdot}HCl$	<1[a]
JF-705	$(C_6H_5)_2C{=}C(Br)COOCH_2CH_2N(C_2H_5)_2{\cdot}HCl$	<1
JF-706	$(C_6H_5)_2C(Cl)COOCH_2CH_2N(C_2H_5)_2{\cdot}HCl$	50[b]
JF-707	$(C_6H_5)_2CHCH(OH)COOCH_2CH_2N(C_2H_5)_2{\cdot}HCl$	±1
JF-708	$(C_6H_5)_2C(OH)CH_2COOCH_2CH_2N(C_2H_5)_2{\cdot}HCl$	<1
JF-709	$(C_6H_5)_2C(OH)CH(OH)COOCH_2CH_2N(C_2H_5)_2{\cdot}HCl$	<1
JF-710	$(C_6H_5)_2C\underset{\backslash\,/}{-}CHCOOCH_2CH_2N(C_2H_5)_2{\cdot}HCl$ (O)	<1
JF-713	$(C_6H_5)_2C(Br)COOCH_2CH_2N(C_2H_5)_2{\cdot}HBr$	63
JF-714	$C_6H_5CH(Br)COOCH_2CH_2N(C_2H_5)_2{\cdot}HBr$	<3
JF-715	$C_6H_5CH(Cl)COOCH_2CH_2N(C_2H_5)_2{\cdot}HCl$	<0.5
JF-717	$(C_6H_5)_2CHC(C_6H_5)(OH)COOCH_2CH_2N(C_2H_5)_2{\cdot}HCl$	---[c]
JF-718	$(C_6H_5)_2CHC(CH_3)(OH)COOCH_2CH_2N(C_2H_5)_2{\cdot}HCl$	<3

(a) 1: <1,000,000
(b) Pharmacological data given by Burtner and Cusic[56] indicate that this substance is an active antispasmodic.
(c) Insoluble.

SUMMARY

The principal object of this investigation was the preparation of basic-alkyl esters, especially β-diethylaminoethyl esters, of certain types of acids in order that they could be examined for pharmacological activity. In addition to the synthesis of these basic esters, it was of interest to prepare certain related compounds, and, for reasons which have been discussed in the General Introduction, to study certain reactions which are mentioned below.

β-Diethylaminoethyl esters of the following acids have been prepared. As far as we are aware, no basic esters of these acids have been described previously.

1. α-chlorophenylacetic acid.
2. α-bromophenylacetic acid.
3. α-bromodiphenylacetic acid.
4. α-ethoxydiphenylacetic acid.
5. α-dimethylaminophenylacetic acid.
6. α-dimethylaminodiphenylacetic acid.
7. α-piperidinophenylacetic acid.
8. α-morpholinophenylacetic acid.
9. β,β-diphenyllactic acid.
10. α,β,β-triphenyllactic acid.
11. α-methyl-β,β-diphenyllactic acid.
12. α,β,β-triphenylacrylic acid.
13. α-bromo-β,β-diphenylacrylic acid.
14. β,β-diphenylglyceric acid.
15. β,β-diphenylglycidic acid.

16. α-methyl-β-phenylglycidic acid.

17. α,β-diphenylglycidic acid.

Acids 14, 15 and 16 are new compounds.

Incidentally, three new derivatives of morpholone-2,

4-ethylmorpholone-2 ethochloride

3-phenyl-4-ethylmorpholone-2 ethobromide

3,3-diphenyl-4-ethylmorpholone-2 ethochloride

as well as ethyl α-(β-diethylaminoethoxy)-β,β-diphenylpropionate hydrochloride, and N-(β-diethylaminoethyl)-diphenylacetamide were obtained.

The statements in the literature regarding ethyl β,β-diphenylglycidate are confusing and contradictory. We have established that a compound which melts at 48-49°, obtained by the condensation of benzophenone and ethyl α-chloroacetate by means of either sodamide or sodium ethylate, is ethyl β,β-diphenylglycidate, and have for the first time obtained the hydrolytic product, β,β-diphenylglycidic acid, in a state of purity.

It has been established that ethyl β,β-diphenylglycidate, under the influence of heat and a small amount of acid, can be isomerized into ethyl diphenylpyruvate. Methyl β,β-diphenylglycidate and β,β-diphenylglycidamide undergo a similar rearrangement to produce methyl diphenylpyruvate and diphenylpyruvamide, respectively.

We have shown that an α-chloronitrile, for example, α-chloroacetonitrile, or a basic ester of an α-chloro acid, such as β-diethylaminoethyl α-chloroacetate, can be employed as the halogen component in the Darzens glycidic ester condensation.

Contrary to the reports in the literature, it has been found possible to prepare diphenylacetaldehyde by the use of the Darzens glycidic ester condensation.

The hitherto unknown diphenylpyruvic acid monohydrate has been described.

In contrast to the reported behavior of ethyl phenylglycidate, we have found that ethyl β,β-diphenylglycidate, upon treatment with ammonia, is converted into the corresponding amide, and not into the amide of an amino acid.

An exception to the Horenstein-Pählicke method for the esterification of an acid with a basic alkyl chloride has been discovered. Thus, interaction of diphenylpyruvic acid and β-diethylaminoethyl chloride in ethanol produces ethyl diphenylpyruvate and β-diethylaminoethanol hydrochloride, and not β-diethylaminoethyl diphenylpyruvate hydrochloride as would be expected.