of crude product. The total yield of crude VII was 0.34 g. (18%). Recrystallization from acetone gave long yellow needles, m.p. 191.5–194.5° dec. See the preceding section, part B, for analysis of compound VII.

Isopropylidene isopropylidenemalonate. To a solution of 3.6 g. (0.025 mole) of isopropylidene malonate in 11.6g. (0.2 mole) of reagent grade acetone were added 5 drops of piperidine and 1 drop of glacial acetic acid. After 12.5 hr. at room temperature, cold water was added to the yellow solution. An oil formed, which upon cooling and scratching, crystallized. Filtration gave 2.65 g. (58%) of crude isopropylidene isopropylidenemalonate, m.p. 70–78°. The crude product was triturated in 5% potassium carbonate solution, filtered, and washed with water to give 0.6 g. (13%) of pure product, m.p. 73–78.5°. Over 2 g. had been lost by this mild treatment. Two recrystallizations accomplished by dissolving the product in methanol and adding water gave the analytical sample, m.p. 75–78.5°.

Anal. Calcd. for $C_9H_{12}O_4$: C, 58.69; H, 6.57. Found: C, 58.78; H, 6.60.

URBANA, ILL.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, VANDERBILT UNIVERSITY]

Small-Ring Heterocyclic Compounds. I. Aldehydes in the Darzens Synthesis of Glycidic Esters[1a]

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The base-catalyzed condensation of ethyl chloroacetate with benzaldehyde gives ethyl *trans*-2,3-epoxy-3-phenylpropanoate (I) contaminated by varying amounts of ethyl *trans*-α-chlorocinnamate. The proportion of the glycidate I is greatest when the cation associated with the base is large, when the solvent is polar, and when the temperature of reaction is about 0–5°. Use of diethylene glycol dimethyl ether, or a combination of higher temperature and polar solvent, results in I which contains a considerable amount of an isomer, possibly the hitherto unreported *cis*-glycidate I. A typical aliphatic aldehyde gave poor results in the Darzens synthesis because of aldol condensation; although formaldehyde also gave poor results, pivalaldehyde, lacking α-hydrogen atoms, gave a glycidic ester in 67% yield. An effort to improve the Darzens condensation by use of a chlorothiol ester was unpromising.

The reaction of benzaldehyde and ethyl chloroacetate in the Darzens condensation produces ethyl 2,3-epoxy-3-phenylpropanoate (I) as the main product. Under the usual conditions employed,[2,3] *trans*-I results,[4] a plausible consequence of "overlap control."[5]

With potassium *t*-butoxide as the base, glycidate I results in good yield and purity.[6] Sodamide, however, results in glycidate I containing about 25% of ethyl α-chlorocinnamate (II).[7] In our hands, incidental use of sodium ethoxide also resulted in a mixture of I and II. These differences in results pointed to the desirability of studying the controlling factors in this typical Darzens condensation.

Table I shows that yields and relative amounts of I and II vary significantly with the base used and with certain of the conditions. As the chlorocinnamate II is not easily separated from the glycidate I by distillation, yields of I and II were calculated

TABLE I

VARIATIONS IN YIELD OF GLYCIDATE I AND CHLOROCINNAMATE II

Expt. No.	Base	Glycidate Yield, %	Ratio of Yields, $\frac{\text{Glycidate I}}{\text{Cinnamate II}}$	Solvent[a]
1	Lithium hydride[b,c]	49	3	E
2	Sodium hydride	61	7	E
3	Lithium ethoxide	85, 65	26, 13	EA
4	Sodium ethoxide[b]	45	6	E and B
5	Sodium ethoxide	49	11	EA
6	Potassium ethoxide	63	13	EA
7	Tetramethylammonium ethoxide	60	100	EA
8	Lithium *t*-butoxide[d]	52	10	TB
9	Potassium *t*-butoxide	71	12	E and TB
10	Potassium *t*-butoxide	61	130	TB
11	Potassium *t*-butoxide[d]	77	45	TB
12	Lithium *t*-pentoxide	38	7	TP

[a] E, ether; EA, ethyl alcohol; B, benzene; TB, *t*-butyl alcohol; TP, *t*-pentyl alcohol. [b] Introduced as the solid. [c] Temperature 53–58°. [d] Reaction effected at room temperature.

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[1] (a) Taken from the Ph.D. dissertation of C. G. C. (January 1961). Research supported in part by the U. S. Army Medical Research and Development Command (Contract No. DA-49-193-MD-2030), and in part by the Office of Ordnance Research, U. S. Army (Contract No. DA-33-008-ORD-1637). (b) Du Pont Postgraduate Teaching Assistant, 1959–1960; N.S.F. Summer Fellow, 1959.

[2] M. S. Newman and B. J. Magerlein, *Org. Reactions*, **5**, 413 (1949). Refs. 2 and 3 are to reviews of the Darzens condensation.

[3] M. Ballester, *Chem. Revs.*, **55**, 283 (1955).

[4] H. O. House, J. W. Blaker, and D. A. Madden, *J. Am. Chem. Soc.*, **80**, 6386 (1958).

[5] (a) H. E. Zimmerman, L. Singer, and B .S. Thyagarajan, *J. Am. Chem. Soc.*, **81**, 108 (1959). (b) H. E. Zimmerman and L. Ahramjian, *J. Am. Chem. Soc.*, **81**, 2086 (1959). (c) H. E. Zimmerman and L. Ahramjian, Meeting of the American Chemical Society, Atlantic City, N. J., September 1959; Abstracts (Organic Division), p. 1P; *J. Am. Chem. Soc.*, **82**, 5459 (1960).

[6] W. S. Johnson, J. S. Belew, L. J. Chinn, and R. Hunt, *J. Am. Chem. Soc.*, **75**, 4995 (1953).

[7] L. Claisen, *Ber.*, **38**, 708 (1905).

from the refractive index of distillate boiling in the range of I and II.

The validity of the analytical method is attested by several facts: infrared spectra of the reaction mixtures contained all of the bands of I and II but no others; the content of II calculated from the chlorine analysis of several samples having a relatively high refractive index (high content of II) agreed reasonably well with the results predicted from the refractive index, as shown by Table II; *trans*-α-chlorocinnamic acid was isolated, after saponification, in 38% yield from a reaction product which had an unusually high content of II (Experiment No. 1 of Table I), thus confirming that II was indeed the contaminant.

In general, the experiments in Table I were patterned after Experiment 10 although there were some variations in molar proportions of reactants and in heating periods, as well as procedural variations necessitated by the physical properties of the reactants. Three conclusions appear to be justified by the results: (a) The ratio of the yield of glycidate I to that of cinnamate II is strongly influenced by the cation of the base used. With the single exception of the anomalous lithium ethoxide reaction, Experiment 3, an increase in the size of the cation with a given anion results in an increase in yield of the glycidate I and an increase especially in the yield of I relative to that of II (compare Experiment 1 with 2; 5 with 6 and 7; 8 with 11). (b) The more polar solvents favor formation of the glycidate (compare Experiment 4 with 5, 9 with 10). (c) An increase in temperature above the usual 0–5° increases the yield of the glycidate I but has a greater effect on the yield of cinnamate II, hence the ratio of I/II decreases (compare Experiment 10 with 11).

TABLE II

PERCENTAGE OF ETHYL α-CHLOROCINNAMATE (II) IN SAMPLES OF I OBTAINED USING DIFFERENT BASES

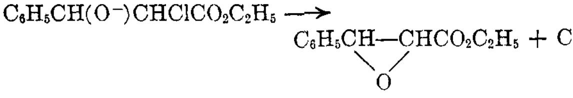
Base	n_D^{25} of Sample	% II Estimated from Refractive Index	Chlorine Analysis
Tetramethylammonium ethoxide	1.5149	1.0	1.4
Sodium ethoxide (Expt. 5)	1.5164	4.2	4.8
Lithium ethoxide	1.5166	4.2	5.4
Potassium *t*-butoxide	1.5171	5.5	7.6
Potassium ethoxide	1.5180	7.5	3.9
Sodium hydride	1.5203	11	17
Lithium *t*-pentoxide	1.5208	13	16
Sodium ethoxide (Expt. 4)	1.5255	22	20
Lithium hydride	1.5303	30	31

For synthesis of glycidate I, a favorable ratio to cinnamate II is more important than the actual yield, owing to the difficult separation. Synthesis of I evidently is best achieved with potassium *t*-butoxide in *t*-butyl alcohol or tetramethylammonium ethoxide in ethanol, at 0–5°. Tetramethylammonium ethoxide, apparently a novel base, obviates the hazard of using potassium; its preparation is somewhat inconvenient, but might be possible *in situ*.[8b]

Significant effects of cations have been observed in several reactions.[8b,9–13] The effects noted in formation of I and II can be explained satisfactorily. The first steps in the Darzens condensation seem analogous to those in the aldol condensation, with the halo ester forming an enolate which attacks the carbonyl component, forming a halohydrin anion.[3] Ordinarily, the halohydrin anion loses halide ion and yields the glycidate.

$$ClCH_2CO_2C_2H_5 + B^- \longrightarrow (ClCHCO_2C_2H_5)^- + BH$$

$$(ClCHCO_2C_2H_5)^- + C_6H_5CHO \longrightarrow C_6H_5CH(O^-)CHClCO_2C_2H_5$$



$$C_6H_5CH(O^-)CHClCO_2C_2H_5 \longrightarrow \underset{\diagdown\ O\ \diagup}{C_6H_5CH{-}CHCO_2C_2H_5} + Cl^-$$

I

Ballester[3] suggests that just as an aldol loses the elements of water to form an unsaturated aldehyde,[14] the halohydrin in the Darzens condensation may form an unsaturated ester, in the present instance the chlorocinnamate II. As the yield of I and the ratio of I : II are strongly influenced by the cation, the equations for the Darzens condensation should be understood to include effects dependent upon the metal ion. The differences among the cations used are essentially in the ionic radii and in the shielding of the positive nuclear charge. The halohydrin anions with different cations accordingly differ in the character of the oxygen-metal bond. The larger cations, forming a more nearly ionic bond, should tend to leave more nearly a full negative charge on the oxygen atom, thereby facilitating rear attack on the α-carbon atom with simultaneous ejection of chloride ion to form glycidate I. The smaller cations forming a more nearly covalent bond, should tend to prevent the internal S_N2 attack and favor elimination to form the chlorocinnamate II.

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[8] (a) The use of benzyltrimethylammonium butoxide has been reported. L. B. Barkley, U. S. Pat. **2,889,320**; *Chem. Abstr.*, **53**, 22094 (1959). (b) Benzyltriethylammonium chloride and other ammonium salts have been used in solutions of sodium ethoxide. M. G. J. Beets and H. Van Essen, *Rec. trav. chim.*, **77**, 1138 (1958).

(9) J. R. Johnson, *Org. Reactions*, **1**, 237–240 (1942).

(10) D. G. Hill, J. Burkus, and C. R. Hauser, *J. Am. Chem. Soc.*, **81**, 602 (1959).

(11) C. R. Hauser and W. H. Puterbaugh, *J. Am. Chem. Soc.*, **75**, 4756 (1953).

(12) D. J. Cram, F. Hauck, K. R. Kopecky, and W. D. Neilsen, *J. Am. Chem. Soc.*, **81**, 5767 (1959). Ref. (7) of this paper contains other references to cation effects.

(13) H. D. Zook and W. L. Gumby, *J. Am. Chem. Soc.*, **82**, 1386 (1960).

(14) For consideration of the loss of OH$^-$ in the aldol condensation, see D. S. Noyce and W. L. Reed, *J. Am. Chem. Soc.*, **81**, 624 (1959).

The observed effects of variation among solvents are consistent with this explanation. Polar solvents should solvate the ions more effectively and enhance the tendency of the oxygen-metal bond to ionize, whereas nonpolar solvents should favor formation of tight ion pairs. The unusual result obtained with lithium ethoxide in Experiment 3 must find its explanation in similar considerations. As this was the only condensation in which the metal chloride did not precipitate, perhaps the dissolved lithium chloride facilitates ring closure by enhancing the tendency of the lithium-oxygen bond to ionize through effects of association or of dielectric constant.

Although the results of Table I indicate that an increase in the reaction temperature by itself or the use of polar solvents at 0° changes only the yield of glycidate and its ratio to II, an additional product is formed by combination of the two conditions, or by the use of diethylene glycol dimethyl ether at 0°. When benzaldehyde and ethyl chloroacetate were condensed in dry dimethylformamide using potassium *t*-butoxide at 27°, the usual glycidate, *trans*-I, was obtained in 29% yield with only a trace of II, along with a large fore-fraction (54% yield). Redistillation of the fore-fraction gave several fractions with identical refractive indexes. This material gave an elementary analysis in excellent agreement with expectation for the glycidate I. It had an infrared spectrum very similar to that of I as ordinarily obtained, but was resolved (barely) into two peaks by gas chromatography. When a sample of the *trans* isomer was injected with the material, the second peak on the chromatogram was intensified, suggesting that one component of the fore-fraction was *trans*-I. Further evidence that the fore-fraction contained *trans*-I was obtained by treating it with dilute sulfuric acid, saponifying the resulting glycol ester, and isolating *threo*-β-phenylglyceric acid identical with the product formed under the same conditions from the commonly obtained *trans*-ester. An effort was made to identify the second component by cautious saponification and fractional crystallization of the sodium salts. This procedure being ineffective, the salts were treated with *p*-nitrobenzylchloride. Chromatography of the ester product gave two substances, but neither was obtained pure. As *trans*-I could not be converted to a *p*-nitrobenzyl ester by the same procedure, perhaps both esters resulted from the second component of the fore-fraction.

The fore-fraction failed to form a 2,4-dinitrophenylhydrazone, showing that the second component of the mixture was not the isomeric ethyl benzoylacetate or ethyl phenylpyruvate (the glycidate I rearranges to the pyruvate under acid catalysis).[4]

The analysis of the fore-fraction proved it to be a mixture of isomers. The narrow range of boiling point and refractive index, and the notable difference in refractive index from I strongly suggest that it is an azeotropic mixture. The most probable isomer of I which is neither an aldehyde nor ketone is ethyl *cis*-2,3-epoxy-3-phenylpropanoate (*cis*-I), a compound which apparently has not been reported. Although *cis*-I was not isolated from the mixture, its formation seems reasonable if one can assume that the higher temperature and polar solvent cause overlap-control in the transition state[5] to become less important. Its presence certainly is consistent with the similarity in infrared spectrum and gas-chromatographic behavior of the fore-fraction and *trans*-I.

An identical fore-fraction was formed[15] (28% yield) using tetramethylammonium ethoxide in the polar solvent ethanol at the increased temperature of 26°. *trans*-I also was isolated (54% yield), along with a trace of II (1% yield).

Diethylene glycol dimethyl ether is a promising solvent for reactions of carbanions.[16] Its use in the Darzens reaction resulted in much of the fore-fraction (30%) however, along with I (37%). It is noteworthy that only diethylene glycol dimethyl ether gave the presumed *cis*-glycidate at 0°.

Another feature of the Darzens condensation, distinct from those discussed above, is that straight chain homologs of acetaldehyde give poor results. The obvious explanation is that the aldehyde undergoes aldol condensation more readily than the Darzens reaction. If this explanation is correct, formaldehyde might undergo effective Darzens condensations since it lacks α-hydrogen atoms. In a test of this possibility, owing to the volatility of formaldehyde and the reactivity of ethyl chloroacetate itself with bases, gaseous formaldehyde and potassium *t*-butoxide were added simultaneously to the chloro ester. However, ethyl 2,3-epoxypropanoate was obtained in a crude yield of only 7%. Generation of formaldehyde within the reaction mixture by the base-catalyzed decomposition of glycolonitrile increased the yield, but only to 17%.

As aldolization could not have led to the unpromising reaction of formaldehyde, it was desirable to determine whether aldolization is indeed responsible for low yields with homologous aldehydes. When propionaldehyde was condensed with ethyl chloroacetate, ethyl 2,3-epoxypentanoate resulted in a crude yield of 25%. The reaction also gave aldol products (54%), as evidenced by physical constants, infrared analysis, and the presence of hydroxyl and carbonyl groups. Inclusive of tar, all of the propionaldehyde used seemed to be accounted for. This result thus demonstrated that aldolization is the principal cause of difficulty

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[15] We are indebted to Dr. C. L. Gladys for this experiment.

[16] H. D. Zook and T. J. Russo, *J. Am. Chem. Soc.*, **82**, 1258 (1960).

with homologs of formaldehyde. Seemingly, therefore, an aliphatic aldehyde with no α-hydrogen atoms, but without the atypically active carbonyl group of formaldehyde, might give a satisfactory Darzens reaction.

The α-carbon of 2,2-dimethyl-4-pentenal bears no hydrogen atoms. Aldolization is precluded, although steric hindrance at the carbonyl group unfortunately is present. This aldehyde, condensed with ethyl chloroacetate, gave ethyl 2,3-epoxy-4,4-dimethylhept-6-eneoate (17%). Ethyl ethoxyacetate also resulted (34%); as it was not found in the previous reactions with benzaldehyde, the rate of condensation with the hindered aldehyde must be considerably slower. Unconsumed aldehyde also resulted.

Better results were obtained with sterically hindered pivalaldehyde and a considerable excess of ethyl chloroacetate. Ethyl 2,3-epoxy-4,4-dimethylpentanoate was obtained in a crude yield of 67%, with no indication of the formation of ethyl *t*-butoxyacetate, thus suggesting that fair yields are obtainable when aldolization is precluded, despite steric hindrance.

In an effort to provide a more reactive ester component, so that the Darzens condensation would compete more favorably with side reactions such as aldolization, phenyl chlorothiolacetate was used. The α-hydrogen atoms of this thiol ester presumably are more acidic than those of phenyl chloroacetate.[17] Phenylchlorothiolacetate and benzaldehyde, however, gave no product which showed a positive test for epoxide with hydriodic acid.[18] Phenyl phenylthiothiolacetate (III) was the only isolable product (11%); it probably was formed as suggested by the equations

$$ClCH_2C(O)SC_6H_5 + C_2H_5OH \longrightarrow ClCH_2C(O)OC_2H_5 + C_6H_5SH$$

$$C_6H_5SH + ClCH_2C(O)SC_6H_5 \longrightarrow \underset{III}{C_6H_5SCH_2C(O)SC_6H_5} + HCl$$

The structure of the previously unknown ester III was suggested by saponification and confirmed by independent synthesis.

EXPERIMENTAL[19]

Ethyl chloroacetate (Kay Fries Chemicals, Inc., New York, N. Y.: n_D^{25} 1.4192) was dried over anhydrous magnesium sulfate and then was considered pure enough for direct use. Glassware used in condensations was dried at 110° overnight, assembled while hot, and protected from moisture with calcium chloride. Unless otherwise indicated, in condensations a solution of the base specified was added dropwise with stirring to a mixture of the aldehyde and ethyl chloroacetate, while the temperature was kept at 0–5°. After the further period of reaction, if any, stated for each experiment, most of the solvent was removed by distillation under reduced pressure. The mixture was poured into water and the product extracted thrice with ether or benzene. The extract was washed with saturated sodium bicarbonate (only if the reaction mixture had been acidified), then with aqueous sodium chloride solution; it was dried over anhydrous sodium sulfate, and largely freed of solvent by warming under reduced pressure. Distillation of the concentrate then was effected using, as specified, a 6-in. Vigreux column, a 18-in. × 6-mm. spinning-band column rated at 23 plates by the manufacturer (Nester and Faust, Wilmington, Del.), or a similar 36-in. × 10-mm. spinning-band column rated at 45 plates. Amounts of I and II were determined by adding the values of each obtained upon using a refractive index-composition plot with all fractions collected in the reported range of boiling point.

Effects of various bases in formation of ethyl 2,3-epoxy-3-phenylpropanoate (I). Benzaldehyde was purified[20] and distilled under nitrogen into ampoules which were sealed until use. A large aliquot of the concentrate of reaction product, isolated as mentioned above, was distilled; weights of product given refer to the mixture of I and ethyl α-chlorocinnamate (II) thus obtained; actual yields of I and II, as given in Table I, were determined from refractive index.

In the comparison given in Table II of "% II Estimated from Chlorine Analysis," the chlorine content of various typical fractions which contained I and II was determined by a modified Stepanow procedure with a Volhard titration.[21]

(1) *Lithium hydride.* Solid lithium hydride (2.4 g.; British Drug Houses, Ltd., Poole, England) was suspended in 300 ml. of anhydrous ether and a mixture of 26.4 g. of benzaldehyde and 36.2 g. of ethyl chloroacetate was added. No gas was evolved, even after addition of 1 ml. of methyl alcohol. The mixture was heated to the reflux temperature (53–58°) for 72 hr., after which no further evidence of hydrogen evolution was discernible, and only trace amounts of hydride remained. The mass was poured into iced hydrochloric acid to decompose any remaining hydride and was extracted as usual. Distillation (6-in. column) gave 31.8 g. of product, b.p. 89–96° (0.5–3.5 mm.), n_D^{25} 1.5246–1.5359 [reported[4] b.p. of I, 96° (0.5 mm.), n_D^{28} 1.5131; also[6] b.p. 168–172° (28 mm.), n_D^{25} 1.5126].

In the demonstration that ethyl *trans*-α-chlorocinnamate (II) was present in reaction mixtures, the product from this experiment was chosen because of its predicted high content of II. Distillate (3.6 g.) of a sample with b.p. 94–95° (0.5 mm.), n_D^{25} 1.5303, was saponified[22] by adding it to sodium (0.4 g.) in absolute ethanol (35 ml.) and then adding water (0.2 g.; more gave no additional precipitate). The salts which precipitated were removed by filtration, dissolved in water and acidified. The glycidic acid decomposed on warming, as evidenced by carbon dioxide evolution. After gas evolution had ceased, the water was extracted with ether, and the ether was extracted with sodium hydroxide solution. After acidification of the basic layer, and recrystallization of the precipitate from hexane, the resulting acid (0.36 g.) melted at 137.5–139° (reported[23] 139–139.5°). This recovery represented 38% of that predicted to be available from the refractive index of the ester mixture. Further recrystallization resulted in material of m.p. 139–140°, undepressed (mixture m.p. 139–140°) by authentic *trans*-α-chlorocinnamic acid.

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[17] M. W. Cronyn, M. P. Chang, and R. A. Wall, *J. Am. Chem. Soc.*, **77**, 3031 (1955).

[18] G. Darzens, *Compt. rend.*, **150**, 1243 (1910). Hydriodic acid forms the α,β-unsaturated ester and molecular iodine, which imparts a yellow-brown color to the solution.

[19] Melting points are corrected and boiling points are uncorrected. C, H, Br, N, and S analyses were by Galbraith Laboratories, Knoxville, Tenn. Infrared spectra were determined with a Model 137 Perkin-Elmer instrument.

[20] L. F. Fieser, *Experiments in Organic Chemistry*, 2nd ed., D. C. Heath and Co., New York, 1941, p. 224.

[21] W. T. Smith, Jr., and R. L. Shriner, *The Examination of New Organic Compounds*, Wiley, New York, 1956, pp. 42–43.

[22] L. Claisen, *Ber.*, **38**, 703 (1905).

[23] C. D. Gutsche and M. Hillman, *J. Am. Chem. Soc.*, **76**, 2236 (1954).

The authentic sample was prepared by the following method: 2,3-dichloro-3-phenylpropionic acid (m.p. 167–168.8°) obtained from cinnamic acid and chlorine[24] was treated with potassium hydroxide[25] to give a mixture of the *cis-* and *trans-*chlorocinnamate salts. The salts were acidified and the acids dissolved in ammonium hydroxide. The *trans* isomer then was precipitated as the barium salt[25] and was converted to the acid (melting point after recrystallization, 139–140°; reported[23] 139–139.5°). The ester (II) was prepared by heating the acid (6.19 g.) in 33 ml. of ethanol containing 1.7 ml. of concd. sulfuric acid; yield after distillation, 4.56 g., n_{D}^{25} 1.5701 (reported[26] 1.5705). The refractive index-composition plot, used in analysis of the products described in experiments 1–15, was prepared using mixtures of II having n_{D}^{25} 1.5701 with I obtained as in (7), n_{D}^{25} 1.5143; the plot was virtually linear.

(2) *Sodium hydride.* A mixture of 26.8 g. of benzaldehyde and 37.2 g. of ethyl chloroacetate was added dropwise during 1.5 hr. to 13.5 g. of 53.8% sodium hydride-in-oil dispersion (Metal Hydrides, Inc.) in 150 ml. of ether. Evolution of hydrogen was steady after a short induction period. After a heating period of 1 hr. on a steam bath, the mass was cooled, acidified, and treated as usual. Distillation of 92% of the extract (6-in. column) gave 30.8 g. of material, b.p. 100–105.5° (0.5 mm.), n_{D}^{25} 1.5175–1.5280.

(3) *Lithium ethoxide.* A solution of 2.08 g. of lithium in 400 ml. of absolute ethyl alcohol[27] was added to 26.0 g. of benzaldehyde and 37.1 g. of ethyl chloroacetate during 1.5 hr. Because of the large volume of ethyl alcohol and the marked solubility of lithium chloride, the reaction remained homogeneous throughout. (In all other condensations, the metal chloride precipitated in the early stages of reaction). The removal of the large excess of solvent required more time than usual; therefore the usual period of stirring after completion of addition of the base was omitted. Distillation (6-in. column) of 95% of the extract gave 30.8 g. of product, b.p. 87–94° (0.9–1.6 mm.), n_{D}^{25} 1.5145–1.5175. (This experiment gave the values of 85% in yield and 26 in ratio listed in Table I).

Repetition of the experiment, except with equimolar amounts (0.34 mole) of the reagents, gave 46.7 g. of product, b.p. 90–96° (0.20–0.35 mm.), n_{D}^{25} 1.5169–1.5207.

(4) *Sodium ethoxide in ether-benzene.* Dry sodium ethoxide (20.9 g.) was added (2.5 hr.) in small portions to 31.8 g. of benzaldehyde and 36.2 g. of ethyl chloroacetate. After about one third of the base had been added, the reaction mass was viscous and 200 ml. of 3:1 ether-benzene was added. After a heating period of 3 hr. on a steam bath, the mixture was acidified and extracted as usual. Distillation (36-in. column) gave 30.2 g. of product, b.p. 134–139° (3.5 mm.), n_{D}^{25} 1.5189–1.5282.

(5) *Sodium ethoxide in ethanol.* A solution of sodium ethoxide containing 7.5 g. of sodium in 125 ml. of absolute ethanol[27] was added during 2 hr. to 31.8 g. of benzaldehyde and 36.2 g. of ethyl chloroacetate. Stirring was continued for 90 min. more while the mixture was heated on a steam bath. The mass was acidified and extracted. Distillation (36-in. column) gave 30.9 g. of product, b.p. 98–102° (0.7 mm.) n_{D}^{25} 1.5141–1.5255.

(6) *Potassium ethoxide.* A solution of 10 g. of oxide-free potassium in 100 ml. of absolute ethanol[27] was added to 26.0 g. of benzaldehyde and 29.6 g. of ethyl chloroacetate over 1.5 hr. The mass was stirred an additional 1.5 hr. and acidified. Distillation of 91% of the ether extract (6-in. column) gave 28.5 g. of product, b.p. 91–93° (0.18–0.35 mm.), n_{D}^{25} 1.5153–1.5212.

(7) *Tetramethylammonium ethoxide at 0–5°.* Tetramethylammonium chloride (30.2 g., dried in an oven at 110°) in 300 ml. of absolute ethanol[27] was added to 6.33 g. of sodium in 200 ml. of ethanol.[27] The mixture was allowed to stand overnight, and sodium chloride was removed by rapid filtration with minimum exposure to the atmosphere. This solution was added within 1.7 hr. to 28.0 g. of benzaldehyde and 34.4 g. of ethyl chloroacetate. After 1 hr. at 25°, tetramethylammonium chloride was separated by filtration and the alcohol removed. After the usual extraction, distillation (6-in. column) gave 30.83 g. of product, b.p. 95–98° (0.45–0.65 mm.), n_{D}^{25} 1.5131–1.5154.

(8) *Lithium t-butoxide.* Lithium (1.8 g.) was heated in about 200 ml. of refluxing dry *t*-butyl alcohol[6] under nitrogen. Since the butoxide was sparingly soluble and formed a fine suspension, the system was stirred continuously to prevent coating of unreacted metal. A mixture of 25.4 g. of benzaldehyde and 30.6 g. of ethyl chloroacetate was added dropwise to the suspension during 1 hr. at 25–30°. After 1 hr. more of stirring, solvent was removed and the residue extracted and washed as usual. Distillation (6-in. column) of 91% of the extract gave product (24.21 g.) having a b.p. of 107–116° (0.8–1.0 mm.), n_{D}^{25} 1.5176–1.5240.

(9) *Potassium t-butoxide at 0° in ether.* Oxide-free potassium (7.5 g.) was dissolved in 200 ml. of dry *t*-butyl alcohol at the reflux temperature. This solution was added dropwise to 21.0 g. of benzaldehyde and 23.4 g. of ethyl chloroacetate in 250 ml. of dry ether during 1.5 hr. The mixture was allowed to stand overnight at 25° and after the usual extraction, distillation (36-in. column) gave 28.3 g. of product, b.p. 101–131° (1–3 mm.), n_{D}^{25} 1.5141–1.5252.

(10) *Potassium t-butoxide at 0° in t-butyl alcohol.* In essentially the procedure of Johnson and co-workers,[6] 9.6 g. of oxide-free potassium in 250 ml. of dry *t*-butyl alcohol was added dropwise to 25.5 g. of benzaldehyde and 29.5 g. of ethyl chloroacetate over 2.5 hr. under nitrogen. The mixture was stirred an additional hour at 25°. Most of the *t*-butyl alcohol was removed and the residue was extracted with ether.

One portion (44%) of the extract was washed with salt solution as usual, dried and distilled (6-in. column); yield, 12.8 g., b.p. 112–119° (1.3 mm.), n_{D}^{25} 1.5133–1 5158.

A second portion (44%) of the ether extract was washed with dilute sulfuric acid and sodium carbonate solution and then treated as before. As the product weighed 12.4 g. and had a b.p. of 112-120° (1.5 mm.), n_{D}^{25} 1.5130–1.5152, there was no advantage in using the acid wash, which has been recommended.[2]

(11) *Potassium t-butoxide at 30° in t-butyl alcohol.* Repetition of Experiment 10 at 29–31° with 4.7 g. of potassium in 100 ml. of *t*-butyl alcohol, 12.7 g. of benzaldehyde, and 14.7 g. of ethyl chloroacetate gave 18.1 g. of product; b.p. 114–117° (1.9–2 mm.), n_{D}^{25} 1.5139–1.5183.

(12) *Lithium t-pentoxide.* A solution of 2.0 g. of lithium in 200 ml. of dry *t*-pentyl alcohol was added dropwise during 1 hr. to 26.9 g. of benzaldehyde and 37.2 g. of ethyl chloroacetate. After an additional 45 min. of stirring at 0°, the mixture was heated for 1 hr. on a steam bath and was extracted. Distillation of 87% of the extract (6-in. column) gave 19.1 g. of product, b.p. 95–114° (0.3-0.5 mm), n_{D}^{25} 1.5193–1.5305.

(13) *Potassium t-butoxide at 27° in dimethylformamide.* Dimethylformamide was dried by adding benzene and distilling, followed by shaking with barium oxide, removing the solid by filtration under nitrogen, and distilling under reduced pressure (n_{D}^{25} 1.4283). A solution of 10.3 g. of potassium in 250 ml. of dry *t*-butyl alcohol was added dropwise to 25.6 g. of benzaldehyde and 31.3 g. of ethyl chloroacetate in 100 ml. of dry dimethyl-formamide at 27° during 2 hr. After removal of the solvent and extraction, two major fractions resulted upon distillation through the 18-in. column. The second fraction, A, consisted of 13.5 g. of the glycidate I (29% yield) and the cinnamate II (0.3% yield), b.p. 76.5–80° (0.4 mm.), n_{D}^{25} 1.5147–1.5148. Fraction B, the fore-fraction,

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(24) E. Erlenmeyer, *Ber.*, **14**, 1867 (1881).

(25) J. J. Sudborough and T. C. James, *J. Chem. Soc.*, **89**, 107 (1906).

(26) E. Walker and T. C. James, *J. Chem. Soc.*, **115**, 1243 (1919).

(27) Prepared using the phthalate method as described in Reference 20, p. 359.

consisted of 24.8 g. (54% yield, assuming B to be a pure isomer of I) of material b.p. 76–96° (0.4–1.3 mm.), n_D^{25} 1.5091–1.5117.

Redistillation of B gave material of constant refractive index, n_D^{25} 1.5097, b.p. 78.5° (0.6 mm).

Anal. Calcd. for $C_{11}H_{12}O_3$: C, 68.73; H, 6.30. Found: C, 69.24; H, 6.65. (Better results were obtained with an identical product from experiment 14.)

Gas chromatography of B on a 4.5 mm. × 3 ft. column containing "Craig Polyester Succinate" (Wilkens Inst. and Research, Inc., Walnut Creek, Calif.) at 155°, helium flow-rate 55 ml./min., showed the presence of two components (retention times 20.0 and 22.0 min.). Admixture of *trans* glycidate I caused an increase in relative intensity of the second peak in the chromatogram. The fact that *trans*-I gave only a single peak under the usual conditions shows that the second peak was not produced by rearrangement or other reaction of the *trans*-I. Treatment of 7.62 g. of B with 30% sulfuric acid according to the procedure of House and Blaker,[28] followed by saponification of the resulting glycol ester, gave an oil which was crystallized from chloroform-isopropyl alcohol (0.34 g., 5% assuming starting ester to be pure *trans*-glycidate I; m.p. 132.5–136°). After several recrystallizations from ether-hexane, the acid had a m.p. of 140–141°, undepressed by authentic *threo-β*-phenylglyceric acid prepared from *trans*-I in 12% yield (reported,[29] m.p. 141–142°). The infrared spectra of the two acids were identical and showed strong absorption at 3500 cm.$^{-1}$ (hydroxyl). Attempts to isolate a second acid from the liquors from B were unsuccessful.

A portion of purified B (9.5 g.) was saponified by the Claisen procedure,[22] which gave 9.0 g. of the sodium salts. Fractional crystallization of the salts in ethanol provided no separation; therefore a 6.5-g. aliquot was dissolved in 10 ml. of water and 20 ml. of ethanol, and 6.5 g. of *p*-nitrobenzyl chloride was added. The mixture was heated under reflux for 2 hr., cooled, diluted with water, and the oily solid (7.7 g.) chromatographed on acid-washed alumina. The original chloride (1.6 g.) was recovered along with two esters; the first had a m.p. of 95–96° after recrystallization (2.7 g.); the second (1.8 g.) resisted crystallization but finally gave a solid with a m.p. of 85–87°. Neither ester was obtained analytically pure. Attempts to prepare the *p*-nitrobenzyl ester of *trans*-I for comparison purposes were unsuccessful.

(14) *Tetramethylammonium ethoxide at 26° in ethanol.*[15] Tetramethylammonium ethoxide was prepared on a large scale in the following manner. Dry tetramethylammonium chloride (114 g.) was dissolved in 1100 ml. of absolute ethanol[27] and 23.3 g. of sodium in 700 ml. of absolute ethanol[27] was added. The sodium chloride was allowed to settle (2 hr.) and the solution was transferred to a dropping funnel through a bent glass tube by means of nitrogen pressure. The sodium chloride was washed with two 100-ml. portions of alcohol and the washings were transferred to the dropping funnel. (Titration with standard acid indicated that less than 1% of the base remained in the flask.) This solution was added to 106 g. of benzaldehyde and 127.5 g. of ethyl chloroacetate over 3.5 hr. at 25–26°. Distillation (36-in. column) provided 53.1 g. (28% yield) of fore-fraction, b.p. 100–105° (1.2 mm.), n_D^{25} 1.5101–1.5128 and 105.8 g of *trans*-I (54% yield) and II (1% yield), b.p. 105–110° (1.2 mm), n_D^{25} 1.5142–1.5153. Redistillation of the fore-fraction provided material identical (infrared spectrum) with B in Experiment 13, n_D^{25} 1.5098.

Anal. Calcd. for $C_{11}H_{12}O_3$: C, 68.73; H, 6.30. Found: C, 68.63; H, 6.31.

(15) *Potassium t-butoxide at 0° in diethylene glycol dimethyl ether.* A solution of 17.9 g. of potassium in 400 ml. of dry *t*-butyl alcohol was added dropwise over 2 hr. to 42.0 g. of benzaldehyde and 56.0 g. of ethyl chloroacetate in 250 ml. of dry diethylene glycol dimethyl ether (distilled from calcium hydride) at 0–5°. Distillation gave 23.0 g. (30% yield) of the fore-fraction B, b.p. 91–96.5° (0.45 mm.), n_D^{25} 1.5097–1.5112; and 28.8 g. of *trans*-I (37% yield) and II (1% yield), b.p. 97.5–99° (0.5 mm.), n_D^{25}1.5151–1.5193. A portion of the fore-fraction (n_D^{25} 1.5097) had an infrared spectrum identical with that of B from Experiments 13 and 14.

Preparation of ethyl 2,3-epoxypropanoate. (a) *From formaldehyde.* A flask containing 28.2 g. of ethyl chloroacetate was fitted with a stirrer, a dropping funnel containing 9.2 g. of potassium in 200 ml. of dry *t*-butyl alcohol, and a pressure valve (a tube immersed 2 cm. in mercury). A connecting flask contained 14 g. of well dried paraformaldehyde, which was decomposed with a soft flame at such a rate that occasionally a bubble escaped through the safety valve. Meanwhile, the base was added dropwise during 1.3 hr. while the reaction mixture was stirred in an ice bath. The ice bath then was removed, formaldehyde added for 15 min. more, and the product isolated as usual. Distillation of the concentrate (6-in. column) gave a middle fraction with a b.p. of 59–90° (15.6 mm.), n_D^{25} 1.4146–1.4188, which gave a positive test for epoxide with hydriodic acid.[18] Redistillation (18-in. column) gave 1.8 g. (7%) of crude ethyl 2,3-epoxypropanoate of b.p. 67–97° (28 mm.), n_D^{25} 1.4124–1.4186 (reported[30] b.p 72–73° (26 mm.), n_D^{30} 1.4150).

(b) *From glycolonitrile.* A mixture of 9.5 g. of glycolonitrile[31] and 19.6 g. of ethyl chloroacetate was added dropwise within 1.5 hr. to a solution of 13.0 g. of potassium in 300 ml. of dry *t*-butyl alcohol and 50 ml. of dry ether at 0–5°. The mixture was allowed to stand overnight and the precipitated salt (24.5 g., 106% of theory of potassium chloride and potassium cyanide) was removed by filtration. Distillation (18-in. column) gave 3.1 g. (17% yield) of ethyl glycidate with a b.p. of 66–78° (10–13 mm.) and n_D^{25} 1.4157–1.4181, which gave a positive test for epoxide,[18] and negative test for chlorine and nitrogen (sodium fusion).

Ethyl 2,3-epoxypentanoate. Potassium (11.4 g.) in 250 ml. of dry *t*-butyl alcohol was added dropwise over 2.2 hr. to 16.9 g. of propionaldehyde (redistilled) and 35.7 g. of ethyl chloroacetate. After the usual treatment, distillation (18-in. column) gave, along with 4.7 g. of tarry residue, essentially two fractions: fraction C (10.4 g., 25% if all were the glycidate), b.p 48–49° (15–16 mm.), n_D^{25} 1.4177–1.4224; fraction D (9.2 g., 54% if all were aldol-type products), b.p. 90–116° (4–16 mm.), n_D^{25} 1.4329–1.4478. Redistillation of C gave 4.9 g. (12%) of ethyl 2,3-epoxypentanoate, b.p. 76–84° (14–16 mm.), n_D^{25} 1.4214–1.4225 (reported[30] b.p. 80° at 15 mm., n_D^{30} 1.4176), which gave a positive epoxide test. Redistillation of D gave 6.03 g. of aldol material, b.p. 38–100° (0.6–2 mm.), n_D^{25} 1.4390–1.4596 (reported[32] b.p. 94° at 20 mm, n_D^{25} 1.4380–1.4500). This material gave positive tests for hydroxyl (pernitratoceric acid[33]) and carbonyl (2,4-dinitrophenylhydrazine). The infrared spectrum (which showed a number of features in common with that of distilled propionaldol[34]) showed hydroxyl absorption (3550 cm.$^{-1}$); double-bond absorption developed (1625 cm.$^{-1}$) after treatment of a sample with 85% phosphoric acid. Fraction C (if considered pure glycidate) would account for 4.2 g. of the starting aldehyde. Fraction D would account for an additional 9.2 g., leaving 3.5 g. to be accounted for in the tarry residue. This balance, however, does not account for all the chloro ester.

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(32) A. T. Nielsen and E. B. W. Ovist, *J. Am. Chem. Soc.*, **76,** 5165 (1954).

(33) F. J. Smith and E. Jones, *A. Scheme of Qualitative Organic Analysis*, Blackie and Son, Ltd., London, 1953, p. 77.

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Ethyl 2,3-epoxy-4,4-dimethylhept-6-eneoate. A solution of 0.5 mole of tetramethylammonium ethoxide in 800 ml. of absolute ethanol[27] was added during 1.5 hr. to 61.3 g. of ethyl chloroacetate and 55.5 g. of redistilled 2,2-dimethyl-4-pentenal.[35] After isolation of product as usual, distillation (36-in. column) provided 16.7 g. (17%) of crude glycidate, b.p. 92.5–102° (4.3 mm.), n_D^{25} 1.4436. Redistillation gave material with a constant n_D^{25} of 1.4447; b.p. 97° (3.0 mm.), d_4^{25} 0.9742, M_D 54.13 (calcd. 53.64).

Anal. Calcd. for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.91; H, 9.36.

Also isolated from the reaction was 22.7 g. of ethyl ethoxyacetate (34% yield), b.p. 56° (15 mm.), n_D^{25} 1.4008, d_4^{25} 0.9637 (reported[36] b.p. 155–158°, n_D^{25} 1.4009), M_D 33.29, (calcd. 33.21).

Anal. Calcd. for $C_6H_{12}O_3$: C, 54.52; H, 9.16; Sapon. equiv., 132. Found: C, 54.20; H, 9.40; Sapon. equiv., 131.

A portion of the distillate obtained upon removal of solvent from the reaction mixture was tested with 2,4-dinitrophenylhydrazine; the test was positive: melting point of the precipitate, 117.5–118° (reported[37] for the hydrazone of the pentenal, 117–118°).

Ethyl 2,3-epoxy-4,4-dimethylpentanoate. A solution of 9.2 g. of potassium in 250 ml. of dry *t*-butyl alcohol was added dropwise to 14.3 g. of redistilled pivalaldehyde (Columbia Organic Chemicals, Inc.) and 29.5 g. of ethyl chloroacetate over 2 hr. at 25°. The next day the mixture was treated as usual. Distillation (36-in. column) gave 19.3 g. (67%), b.p. 81° (5–9 mm.), n_D^{25} 1.4232–1.4264. Redistillation provided 8.7 g. (30%) of ethyl 2,3-epoxy-4,4-dimethylpentanoate, b.p. 57–65° (3 mm.), n_D^{25} 1.4253–1.4258. A third distillation gave material of constant n_D^{25} 1.4255, b.p. 68° (4 mm.), d_4^{25} 0.9648, M_D 45.68 (calcd. 44.86). The product gave a positive epoxide test with hydriodic acid and no precipitate with 2,4-dinitrophenylhydrazine.

Anal. Calcd. for $C_9H_{16}O_3$: C, 62.78; H, 9.35; Sapon. equiv., 172. Found: C, 62.70; H, 9.51; Sapon. equiv., 175.

Reaction of benzaldehyde, phenyl chlorothiolacetate, and potassium t-butoxide. Potassium *t*-butoxide (0.09 mole) in *t*-butyl alcohol was added (1 hr.) to benzaldehyde (9.1 g.) and phenyl chlorothiolacetate[38] (16.0 g.) in ether at 0°. After 1 hr., the usual isolation, two distillations (6-in. column), and chilling resulted in 11% of greasy phenyl phenylthiothiolacetate (III). Recrystallization gave colorless III, m.p. 63.5–65°. No other substance was isolated.

With anhydrous potassium acetate in dry ethanol (or methanol) as the base, the yield of recrystallized III, b.p. 185° (0.9 mm.), was 56%, m.p. 64–65°.

Anal. Calcd. for $C_{14}H_{12}OS_2$: C, 64.58; H, 4.65; Sapon. equiv. 130. Found: C, 64.25; H, 5.25; Sapon. equiv. 128.

Interestingly, under the same conditions in the absence of benzaldehyde, no III was isolated.

III was saponified[22] by adding 1 equivalent to 2 g.-atom proportions of sodium in absolute ethanol,[27] followed by 1 equivalent of water. The resulting salt was acidified and the phenylthioacetic acid ($C_6H_5SCH_2CO_2H$) recrystallized (hexane); m.p. and mixture m.p., 64.5–65.5°; anilide, m.p. 81.5–82.5° (Kofler hot stage) (reported,[39] 82–83°); *p*-bromophenacyl ester, m.p. 87–88°.

Anal. Calcd. for $C_{16}H_{13}BrO_3S$: Br, 21.88. Found: Br, 21.46.

For synthesis of III, benzenethiol (2.20 g.) was dissolved in 20 ml. of absolute ethanol containing 0.02 mole of potassium ethoxide, and phenyl chlorothiolacetate (2.00 g.) in 15 ml. of ethanol was added. Potassium chloride was separated. The filtrate was warmed slightly, and cooled. Upon addition of water, III precipitated. After two recrystallizations from hexane, the m.p. was 64–65°, undepressed by the product from the potassium acetate reaction; yield, 10%.

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[35] We wish to thank Dr. J. B. Dickey of the Tennessee Eastman Corp., Kingsport, Tenn., for providing this material.

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[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, AGRICULTURAL CHEMICALS DIVISION, MONSANTO CHEMICAL CO.]

The Darzens Condensation. I. Reaction of Chloroacetamides with Acetone and Cyclohexanone

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Ethyl chloroacetate undergoes the Darzens condensation with acetone or cyclohexanone regardless of basic agents used. In contrast, *N,N*-diethyl-α-chloroacetamide, presumably because of the relatively lower acidity of its α-hydrogens, does not readily undergo the Darzens condensation. Instead, γ-keto amides are produced as the predominant product. These arise from displacement of the chlorine by the enolates of acetone and cyclohexanone when either potassium *t*-butoxide or sodium hydride is used. If either methoxide or ethoxide is used, the same products are formed along with α-alkoxy amides.

The Darzens glycidic ester condensation[1] has been applied to only a few α-chloro amides.[1a,2] However, some discrepancies were noted in some of the glycidamide work. Fourneau[2a] reported a 55% yield of 3,3-dimethylglycidamide (Ia) (m.p. 85–87°) from acetone and chloroacetamide when sodium ethoxide was used as the condensing agent, but von Schickh[2b] reported an 80% yield (m.p. 121°) when metallic sodium was used. Forneau[2a] also stated that 3,3-diethylglycidamide, prepared from diethyl ketone and chloroacetamide, melted at 148°. However, he also reported a melting point

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