Organic Syntheses

A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

# Working with Hazardous Chemicals

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*These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.*

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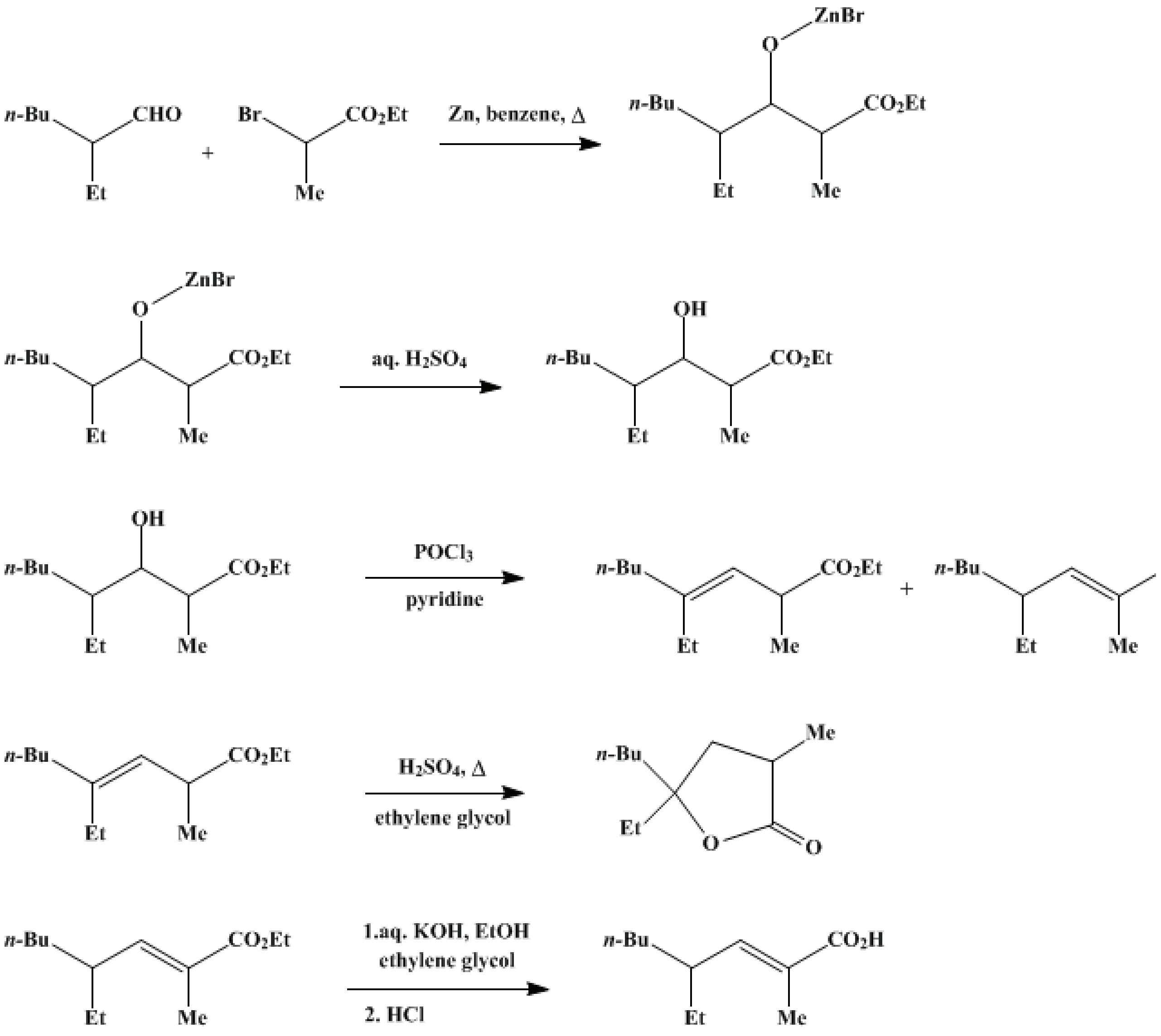
# 4-ETHYL-2-METHYL-2-OCTENOIC ACID

## [2-Octenoic acid, 4-ethyl-2-methyl-]



Submitted by Kenneth L. Rinehart, Jr. and Edward G. Perkins[1].
Checked by Melvin S. Newman and Joseph H. Manhart.

## 1. Procedure

A 3-l. three-necked flask is equipped with a mercury-sealed mechanical stirrer prepared from tantalum wire, a condenser arranged for distillation, and a 500-ml. pressure-equalizing dropping funnel. The flask is heated on a steam cone, and a slow stream of nitrogen is introduced from a cylinder through a line connected to the top of the dropping funnel. To the flask are added 98.1 g. (1.50 g. atoms) (Note 1) of freshly sandpapered zinc foil which has been cut into narrow strips and rolled loosely, and 750 ml. of thiophene-free benzene previously dried over sodium. To dry the apparatus and contents, 175–200 ml. of benzene is slowly distilled with stirring. Heating is interrupted, and the condenser is quickly arranged for reflux. A U-tube just closed with mercury is attached to the top of the condenser, and nitrogen flow is adjusted so that it bubbles slowly through the mercury. The benzene is heated once again to reflux, and a solution of 64.1 g. (0.50 mole) of 2-ethylhexanal (Note 2) and 271.5 g. (1.50 moles) of ethyl α-bromopropionate *(Caution! (Note 3))* in 500 ml. of dried benzene is placed in the dropping funnel. The first 50 ml. of the solution is added to the flask at once. Usually reaction begins immediately, as evidenced by darkening of the zinc surface and clouding of the solution, but in some cases as much as 15 minutes elapses before the start of reaction. When the reaction has started, the remainder of the aldehyde-bromo ester solution is added during 1 hour, with stirring, as the solution is maintained under reflux. After addition is complete the mixture is heated for an additional 2 hours under reflux, and then cooled to room temperature.

The nitrogen line is removed, and to the solution is added 750 ml. of 12*N* sulfuric acid; the resulting mixture is stirred vigorously for 1 hour, and then decanted into a 3-l. separatory funnel. After the two phases have separated, the lower aqueous layer is drawn off into a 3-l. separatory funnel containing 1 l. of water which has been used to wash the reaction flask, and the diluted mixture is extracted twice with 350-ml. portions of benzene which have also been employed to rinse the reaction flask. The original organic layer and the combined benzene extracts are kept separate and are washed successively with 500-ml. portions of water, saturated sodium bicarbonate solution, and again with water. The two organic portions are now combined, allowed to stand over anhydrous sodium sulfate until clear, then transferred to a 2-l. distilling flask, from which solvent is distilled at atmospheric pressure, last traces under aspirator pressure. The residue remaining in the flask weighs 150–165 g. (Note 4) and is dehydrated without further purification.

To the residue which contains the crude hydroxy ester there is added 710 g. of pyridine (commercial reagent, C.P. grade), and the mixture is cooled to about 5° in an ice bath. To the cooled solution is added slowly with vigorous swirling 155 g. of phosphorus oxychloride (commercial reagent, C.P.); white crystals form almost immediately. The mixture is allowed to stand 8 hours at room temperature and is finally heated for 1.5 hours on the steam bath (Note 5). It is then cooled to room temperature and decanted into a 5-l. separatory funnel containing 1.25 kg. of cracked ice. Crystals that remain in the flask are decomposed with an additional 125 g. of ice. The flask is rinsed with 1.5 l. of water, and then with 400 ml. of hexane. These washes are added to the material in the separatory funnel. After the two layers have been shaken together thoroughly and then separated, the aqueous phase is extracted with two additional 400-ml. portions of fresh hexane. The three hexane extracts are not combined, but are washed in turn with two 500-ml. portions of 2*N* hydrochloric acid to remove pyridine. Excess hydrochloric acid is removed by washing with three 200-ml. portions of water to pH 4. The clear amber-colored solution is dried over anhydrous sodium sulfate, and solvent is removed by distillation as before. The residue, which weighs 120–135 g. and consists mainly of ethyl 4-ethyl-2-methyl-2-(and-3-) octenoates, is not distilled but is heated with sulfuric acid to convert the $\Delta^3$-isomer to γ-lactone (Note 6), (Note 7), and (Note 8).

To the residue is added 600 ml. of ethylene glycol, followed by 40 ml. of concentrated sulfuric acid. The resulting mixture is heated under vigorous reflux for 20 hours, and then cooled and transferred to a 2-l. stainless-steel or copper flask. To this material is added a solution prepared from 325 g. of potassium hydroxide, 300 ml. of water, and 300 ml. of 95% ethanol. The resultant solution is heated under reflux for 1 hour, and then cooled and transferred to a 5-l. separatory funnel, where it is diluted with 3 l. of water and acidified with 600 ml. of concentrated hydrochloric acid. The organic liquid which separates is diluted with 300 ml. of hexane and separated from the aqueous layer, which is extracted three additional times with 300-ml. portions of hexane. The hexane extracts are washed to pH 4 with three 300-ml. portions of water, and then combined and dried over anhydrous sodium sulfate. For removal of solvent by flash distillation, a 150-ml. round-bottomed flask, equipped with a ground joint attached to a distillation head and side tubulature attached to a dropping funnel, is heated by an oil bath whose temperature is maintained at 130–140°. After all the solution has been added at about the rate of distillation, the dropping funnel is replaced by a capillary, and the last of the solvent is removed at reduced pressure furnished by a water pump. The flask is finally attached to an efficient fractionating column (Note 9), and the residue of mixed α,β-unsaturated acid and γ-lactone is distilled carefully at reduced pressure. After 1–5 g. of fore-run, there are obtained 25–28.5 g. (27–31%) of 4-ethyl-4-hydroxy-2-methyloctanoic acid, γ-lactone, b.p. 118–121°/5.0 mm., $n_{\mathrm{D}}^{25}$ 1.4469–1.4473 (Note 10), 2–3 g. of intermediate, and 27.5–32 g. (30–35%) of 4-ethyl-2-methyl-2-octenoic acid, b.p. 140–143°/5.0 mm., $n_{\mathrm{D}}^{25}$ 1.4613–1.4625 (Note 11).

## 2. Notes

1. The yield in this reaction is improved by an excess of zinc and bromo ester relative to aldehyde. The present ratio of zinc:bromo ester:aldehyde (3:3:1) gives 87% of intermediate β-hydroxy ester; when the ratio is reduced to 2:3:1, the yield is lowered to about 68%.

2. Commercially available 2-ethylhexanal (Eastman practical grade) is purified by fractional distillation; b.p. 163–163.2°/atm., $n_D^{25}$ 1.4133. Other aldehydes are conveniently prepared by the Rosenmund reduction.[2] If the aldehyde is relatively unstable toward autoxidation,[3] a catalytic amount (0.5–1.0 g.) of hydroquinone is added with the aldehyde-bromo ester solution.

3. Ethyl α-bromopropionate is available commercially (Sapon Laboratories, $n_D^{25}$ 1.4452) and is employed without purification. *Bromo esters are severe lachrymators, and operations that involve transferring these compounds from one vessel to another should be conducted in a well-ventilated hood.*

4. If ethyl 4-ethyl-2-methyl-3-hydroxyoctanoate is isolated by distillation of this residue, the yield is about 100 g. (87%), b.p. 122–124°/4.9 mm., $n_D^{25}$ 1.4415.

5. During heating, the mixture becomes dark brown; however, most of the color is removed by subsequent washing with hydrochloric acid. If terminal heating is omitted, the yield in the dehydration step is reduced by approximately 15%.

6. If no separation of isomers is required, as when the mixture is to be hydrogenated, the mixed esters may be obtained by distillation; yield 75–90 g. (71–85%, based on starting aldehyde). It is extremely difficult to separate the $\Delta^2$- from the $\Delta^3$-ester by fractional distillation, as the two boil only 7° apart; however, by careful fractionation and refractionation through an 0.8 × 125-cm. simple Podbielniak column with partial-reflux head,[4] it is possible to obtain[3] pure ethyl 4-ethyl-2-methyl-2-octenoate, b.p. 102–103°/4.8 mm., $n_D^{25}$ 1.4478, and a nearly pure sample of ethyl 4-ethyl-2-methyl-3-octenoate, b.p. 94–95°/4.8 mm., $n_D^{25}$ 1.4393.

7. When α,γ-dialkyl-β,γ-unsaturated esters and acids are heated with acid, they are slowly converted to γ-lactones. The corresponding α,β-unsaturated isomers are recovered unchanged.[3] Treating a mixture of the two isomeric esters or acids with sulfuric acid in refluxing glycol thus destroys the unconjugated isomer, while leaving the conjugated compound intact. Whereas the isomeric esters and acids have very similar boiling points (Note 6), the γ-lactone boils 20–25° lower than the $\Delta^2$-acid and thus may be separated easily from the acid by fractional distillation. The acid may also be extracted from the lactone with sodium carbonate, or its barium salt may be precipitated by methanolic barium hydroxide.

Lactonization as a means of obtaining $\Delta^2$-acid free from $\Delta^3$-isomer is useful for unsaturated acids or esters having an α-alkyl substituent. Conjugated acids or esters without an α-alkyl substituent undergo acid-catalyzed isomerization to the $\Delta^3$-isomer and subsequent lactonization with loss in yield of the $\Delta^2$-compound.[5] In the latter case, use may be made of the differential rate either of bromine addition[6] or of esterification[3] for the conjugated and unconjugated compounds as a means of obtaining pure conjugated acid.

8. In the present case, the proportion of $\Delta^2$-isomer in the original dehydration mixture may be estimated to be 42% of the total unsaturated esters, while an equilibrium mixture contains about 67% of the conjugated compound.[3] Thus the amount of conjugated isomer in the mixture may be considerably increased by base-catalyzed isomerization of the unsaturated esters. For other unsaturated esters, both the composition of the dehydration mixture[3,7] and the equilibrium ratio of the two isomers[3,8] vary, depending on the position and nature of alkyl substituents on the chain, and equilibration is not always desirable. For suitable compounds the following procedure is advantageous; scrupulous protection against moisture is essential.

A 2-l. round-bottomed flask is fitted with a coil condenser (cooling water *inside* the coil) having a large free space in the center and is protected from atmospheric moisture by a calcium chloride tube. The apparatus is dried thoroughly with a Bunsen burner, and 1.5 l. of commercial ethylene glycol is introduced into the flask, together with 50 ml. of diethyl phthalate. The glycol is heated (with salt bath or electric mantle) to a temperature slightly under reflux, the calcium chloride tube is removed, and 50 g. of sodium is added cautiously, in suitable pieces, through the condenser. It is necessary to wait after the addition of each piece, for sodium melts at these temperatures and dissolves in glycol exothermically with vigorous evolution of hydrogen. After all the sodium has been added, the solution is heated for 1 hour under reflux. The condenser is arranged for distillation into a graduated thoroughly dried pressure-equalizing dropping funnel, and, as before, the system is protected by a calcium chloride tube. Heating is resumed, and the first 300 ml. of distilled glycol, which contains any remaining water, is discarded. The separatory funnel is replaced by a 1-l. stainless-steel flask with standard taper joint, which has been thoroughly dried with a burner. In this flask is collected the next 750 ml. of distilled glycol. The condenser and a calcium chloride tube are transferred to the steel flask, the contents are heated to a temperature slightly under boiling, and 57.5 g. of sodium is added in large pieces as before. The residue of unsaturated esters is introduced from a large pipet, a boiling chip is added, and the mixture is heated for 20 hours under reflux. It is then cooled to room temperature and decanted cautiously into a 2-l. round-bottomed flask containing a mixture of 210 ml. of glycol and 70 ml. of concentrated sulfuric acid. To the flask is added an additional 70 ml. of concentrated sulfuric acid, and after the mixture has been heated under reflux for 12 hours it is worked up as described in the final paragraph of the main procedure. Upon fractional distillation of the products, there are obtained 17.5–23.9 g. (19–26%) of 4-ethyl-4-hydroxy-2-methyloctanoic acid, γ-lactone, and 34.1–39.6 g. (38–43%) of 4-ethyl-2-methyl-2-octenoic acid. In this instance, therefore, the yield of $\Delta^2$-acid is increased approximately one-third by isomerizing the dehydration products before converting the $\Delta^3$-acid to lactone.

9. An 0.8 × 125-cm. simple Podbielniak column[4] with partial reflux head is a suitable type.

10. An analytical sample of 4-ethyl-4-hydroxy-2-methyloctanoic acid, γ-lactone, has b.p. 115–117°/4.3 mm., $n_D^{25}$ 1.4462.

11. An analytical sample of 4-ethyl-2-methyl-2-octenoic acid has b.p. 141–142°/4.6 mm., $n_D^{25}$ 1.4628.

## 3. Discussion

The procedure employed has been previously described by Cason and Rinehart[3] and is a modification of the standard Reformatsky procedure.[9,10] The Reformatsky reaction, which has been reviewed elsewhere,[9] has been widely employed with ketones, somewhat less frequently with aldehydes, and very seldom with α-alkyl aliphatic aldehydes.

4-Ethyl-2-methyl-2-octenoic acid has been prepared only by this method. An alternative synthesis of α-alkyl-α,β-unsaturated acids proceeds via α-bromination of the saturated acid, followed by dehydrohalogenation with quinoline at elevated temperatures.[11] The present method is especially well adapted to preparation of α,γ-dialkyl-α,β-unsaturated acids.

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## References and Notes

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## Appendix
## Chemical Abstracts Nomenclature (Collective Index Number);
## (Registry Number)

glycol

ethanol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

hydrogen (1333-74-0)

hydroquinone (123-31-9)

sodium bicarbonate (144-55-8)

sodium carbonate (497-19-8)

bromine (7726-95-6)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

mercury (7439-97-6)

Phosphorus Oxychloride (21295-50-1)

pyridine (110-86-1)

potassium hydroxide (1310-58-3)

zinc,
zinc foil (7440-66-6)

sodium (13966-32-0)

ethylene glycol (107-21-1)

barium hydroxide (17194-00-2)

Quinoline (91-22-5)

ethyl α-bromopropionate (535-11-5)

hexane (110-54-3)

diethyl phthalate (84-66-2)

4-ETHYL-2-METHYL-2-OCTENOIC ACID,
2-Octenoic acid, 4-ethyl-2-methyl- (6975-97-9)

2-ethylhexanal (123-05-7)

4-ethyl-4-hydroxy-2-methyloctanoic acid, γ-lactone

Ethyl 4-ethyl-2-methyl-3-hydroxyoctanoate

ethyl 4-ethyl-2-methyl-2-octenoate

ethyl 4-ethyl-2-methyl-3-octenoate