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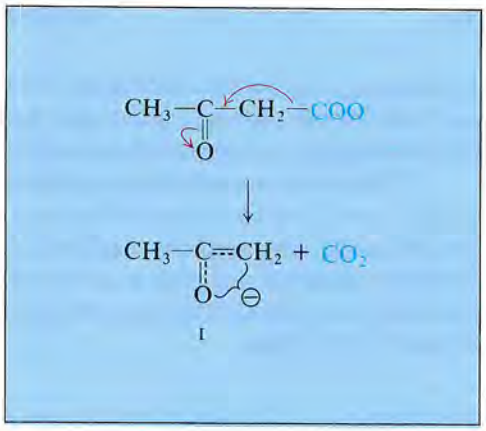


Carbanions II

Malonic Ester and Acetoacetic Ester Syntheses

25.1 Carbanions in organic synthesis

We have already seen something of the importance to organic synthesis of the formation of carbon–carbon bonds: it enables us to make big molecules out of little ones. In this process a key role is played by negatively charged carbon. Such *nucleophilic carbon* attacks carbon holding a good leaving group—in alkyl halides or sulfonates, usually—or carbonyl or acyl carbon. Through nucleophilic substitution or nucleophilic addition, a new carbon–carbon bond is formed.

Nucleophilic carbon is of two general kinds. (a) There are the carbanion-like groups in organometallic compounds, usually generated through reaction of an organic halide with a metal: Grignard and organolithium reagents, for example. (b) There are the more nearly full-fledged carbanions generated through abstraction of α-hydrogens by base, as in the aldol and Claisen condensations and their relatives.

The difference between these two kinds of carbon is one of degree, not kind. There is interaction—just how much depending on the metal and the solvent—even between electropositive ions like sodium or potassium or lithium and the anion from carbonyl compounds. These intermediates, too, could be called organometallic compounds; the bonding is simply more ionic than that in, say, a Grignard reagent.

In this chapter we shall continue with our study of carbanion chemistry, with emphasis on the attachment of alkyl groups to the α-carbons of carbonyl and acyl compounds. Such *alkylation* reactions owe their great importance to the special nature of the carbonyl group, and in two ways. First, the carbonyl group makes α-

hydrogens acidic, so that alkylation can take place. Next, the products obtained still contain the carbonyl group and hence are highly reactive; they are ideal intermediates for *further* molecule-building.

Of the very many alkylation methods that have been developed, we can look at only a few: first, two classics of organic synthesis, the *malonic ester synthesis* and the *acetoacetic ester synthesis*; and then, several newer methods. In doing this we shall be concerned not only with learning a bit more about how to make new molecules from old ones, but also with seeing the variety of ways in which carbanion chemistry is involved.

25.2 Malonic ester synthesis of carboxylic acids

One of the most valuable methods of preparing carboxylic acids makes use of ethyl malonate (*malonic ester*), $CH_2(COOC_2H_5)_2$, and is called the **malonic ester synthesis**. This synthesis depends upon (a) the high acidity of the α-hydrogens of malonic ester, and (b) the extreme ease with which malonic acid and substituted malonic acids undergo decarboxylation. (As we shall see, this combination of properties is more than a happy accident, and can be traced to a single underlying cause.)

Like acetoacetic ester (Sec. 21.11), and for exactly the same reason, malonic ester contains α-hydrogens that are particularly acidic: they are *alpha* to *two* carbonyl groups. When treated with sodium ethoxide in absolute alcohol, malonic ester is converted largely into its salt, *sodiomalonic ester*:

$$\underset{\text{Stronger acid}}{H{-}CH(COOC_2H_5)_2} + Na^+{}^-OC_2H_5 \rightleftharpoons \underset{\text{Sodiomalonic ester}}{CH(COOC_2H_5)_2{}^-Na^+} + \underset{\text{Weaker acid}}{H{-}OC_2H_5}$$

Reaction of this salt with an alkyl halide yields a substituted malonic ester, an *ethyl alkylmalonate*, often called an *alkylmalonic ester*:

$$CH(COOC_2H_5)_2{}^-Na^+ + R{-}X \longrightarrow \underset{\substack{\text{Ethyl alkylmalonate}\\ \text{An alkylmalonic ester}}}{R{-}CH(COOC_2H_5)_2} + Na^+X^-$$

This reaction involves nucleophilic attack on the alkyl halide by the carbanion, $CH(COOC_2H_5)_2{}^-$, and, as we might expect, gives highest yields with primary alkyl halides, lower yields with secondary alkyl halides, and is worthless for tertiary alkyl halides and for aryl halides.

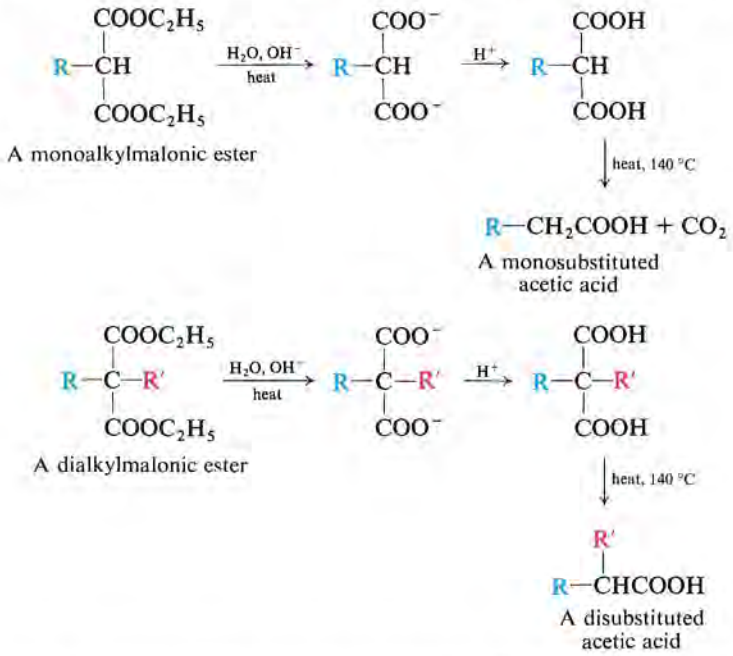
The alkylmalonic ester still contains one ionizable hydrogen, and on treatment with sodium ethoxide it, too, can be converted into its salt; this salt can react with an alkyl halide—which may be the same as, or different from, the first alkyl halide—to yield a dialkylmalonic ester:

$$R{-}CH(COOC_2H_5)_2 + Na^+{}^-OC_2H_5 \rightleftharpoons R{-}C(COOC_2H_5)_2{}^-Na^+ + C_2H_5OH$$

$$\downarrow R'X$$

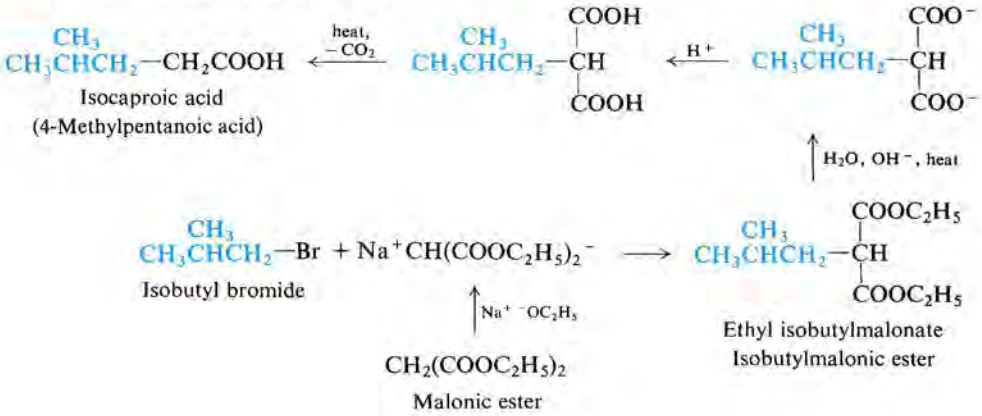
$$\underset{\text{A dialkylmalonic ester}}{\begin{matrix} & R' & \\ & | & \\ R{-}C(COOC_2H_5)_2 & + & Na^+X^- \end{matrix}}$$

The acidity of malonic ester thus permits the preparation of substituted malonic esters containing one or two alkyl groups. Now, how can these substituted malonic esters be used to make carboxylic acids? When heated above its melting point, malonic acid readily loses carbon dioxide to form acetic acid; in a similar way substituted malonic acids readily lose carbon dioxide to form substituted acetic acids. The monoalkylmalonic and dialkylmalonic esters we have prepared are readily converted into monocarboxylic acids by hydrolysis, acidification, and heat:

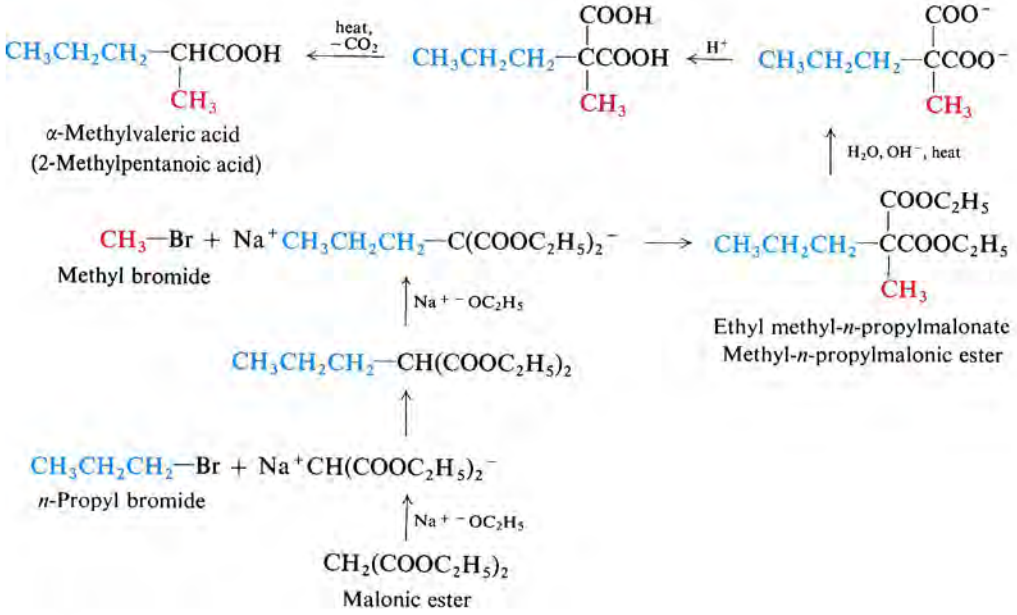


A malonic ester synthesis yields an acetic acid in which one or two hydrogens have been replaced by alkyl groups.

In planning a malonic ester synthesis, our problem is to select the proper alkyl halide or halides; to do this, we have only to look at the structure of the acid we want. Isocaproic acid, for example, $(CH_3)_2CHCH_2CH_2COOH$, can be considered as acetic acid in which one hydrogen has been replaced by an isobutyl group. To prepare this acid by the malonic ester synthesis, we would have to use isobutyl bromide as the alkylating agent:

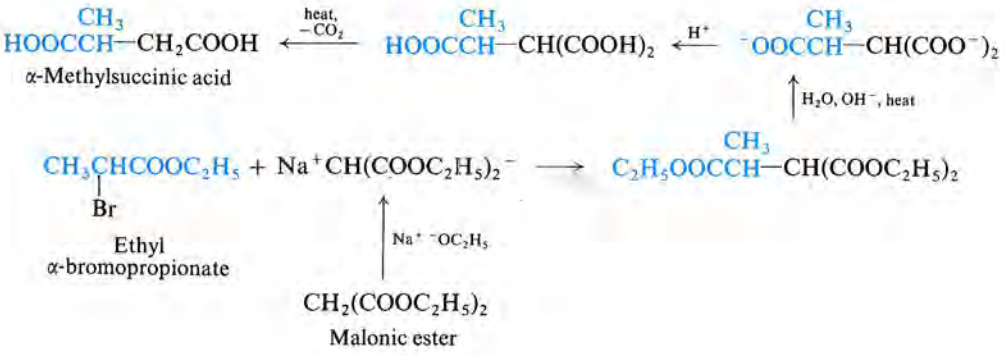


An isomer of isocaproic acid, α-methylvaleric acid, $CH_3CH_2CH_2CH(CH_3)COOH$, can be considered as acetic acid in which one hydrogen has been replaced by a *n*-propyl group and a second hydrogen has been replaced by a methyl group; we must therefore use two alkyl halides, *n*-propyl bromide and methyl bromide.



The basic malonic ester synthesis we have outlined can be modified. Often one can advantageously use: different bases as, for example, potassium *tert*-butoxide; alkyl sulfonates instead of halides; polar aprotic solvents like DMSO or DMF (Sec. 7.4).

In place of simple alkyl halides, certain other halogen-containing compounds may be used, in particular the readily available α-bromo esters (why can α-bromo *acids* not be used?), which yield substituted succinic acids by the malonic ester synthesis. For example:



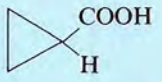
Problem 25.1 Outline the synthesis of each of the following compounds from malonic ester and alcohols of four carbons or fewer:

(a) the isomeric acids, *n*-valeric, isovaleric, and α-methylbutyric. (Why can the malonic ester synthesis not be used for the preparation of trimethylacetic acid?)
(b) *leucine* (α-aminoisocaproic acid) (c) *isoleucine* (α-amino-β-methylvaleric acid)

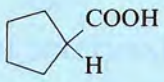
Problem 25.2 *Adipic acid* is obtained from a malonic ester synthesis in which the first step is addition of one mole of ethylene bromide to a large excess of sodiomalonic ester in alcohol. *Cyclopropanecarboxylic acid* is the final product of a malonic ester synthesis in which the first step is addition of one mole of sodiomalonic ester to two moles of ethylene bromide followed by addition of one mole of sodium ethoxide.

$HOOCCH_2CH_2CH_2CH_2COOH$

Adipic acid



Cyclopropane-carboxylic acid



Cyclopentane-carboxylic acid

(a) Account for the difference in the products obtained in the two syntheses. (b) Tell exactly how you would go about synthesizing *cyclopentanecarboxylic acid*.

Problem 25.3 (a) Malonic ester reacts with benzaldehyde in the presence of piperidine (a secondary amine, Sec. 30.12) to yield a product of formula $C_{14}H_{16}O_4$. What is this compound, and how is it formed? (This is an example of the **Knoevenagel reaction**.) (b) What compound would be obtained if the product of (a) were subjected to the sequence of hydrolysis, acidification, and heating? (c) What is another way to synthesize the product of (b)?

Problem 25.4 (a) Cyclohexanone reacts with cyanoacetic ester (ethyl cyanoacetate, $N{\equiv}CCH_2COOC_2H_5$) in the presence of ammonium acetate to yield a product of formula $C_{11}H_{15}O_2N$. What is this compound, and how is it formed? (This is an example of the **Cope reaction**.) (b) What compound would be formed from the product of (a) by the sequence of hydrolysis, acidification, and heating?

Problem 25.5 In an example of the **Michael condensation**, malonic ester reacts with ethyl 2-butenoate in the presence of sodium ethoxide to yield A, of formula $C_{13}H_{22}O_6$. The sequence of hydrolysis, acidification, and heating converts A into 3-methylpentanedioic acid. What is A, and how is it formed? (*Hint*: See Sec. 11.22. Check your answer in Sec. 27.7.)

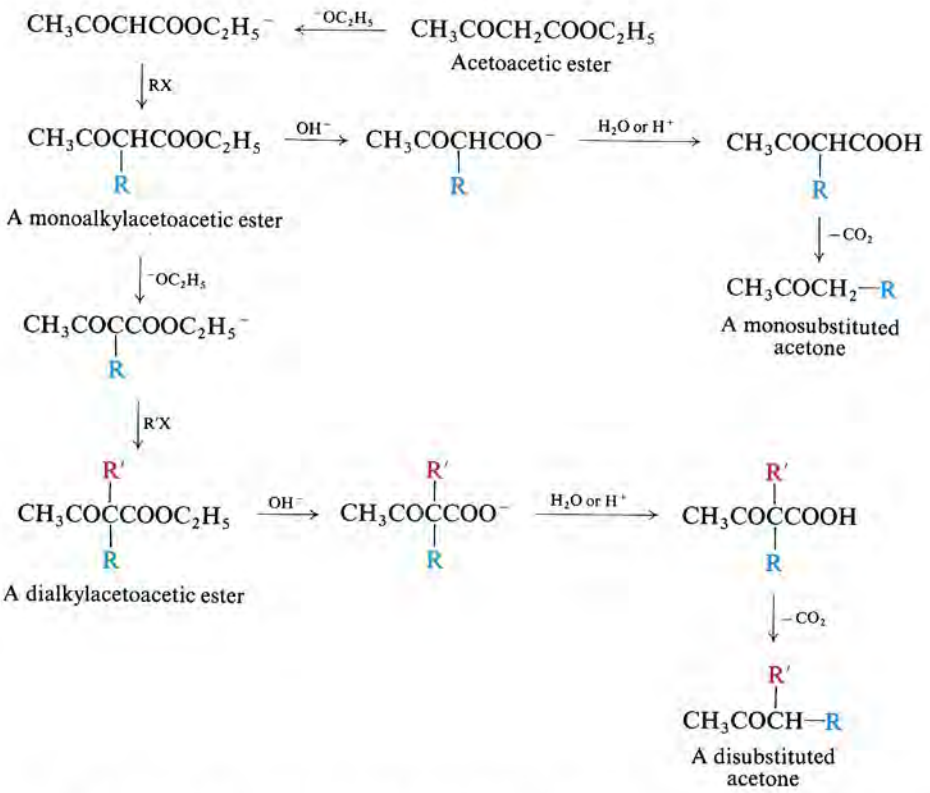
25.3 Acetoacetic ester synthesis of ketones

One of the most valuable methods of preparing ketones makes use of ethyl acetoacetate (*acetoacetic ester*), $CH_3COCH_2COOC_2H_5$, and is called the **acetoacetic ester synthesis of ketones**. This synthesis closely parallels the malonic ester synthesis of carboxylic acids.

Acetoacetic ester is converted by sodium ethoxide into the sodioacetoacetic ester, which is then allowed to react with an alkyl halide to form an alkylacetoacetic ester (an ethyl alkylacetoacetate), $CH_3COCHRCOOC_2H_5$; if desired, the alkylation can be repeated to yield a dialkylacetoacetic ester, $CH_3COCRR'COOC_2H_5$. All alkylations are conducted in absolute alcohol.

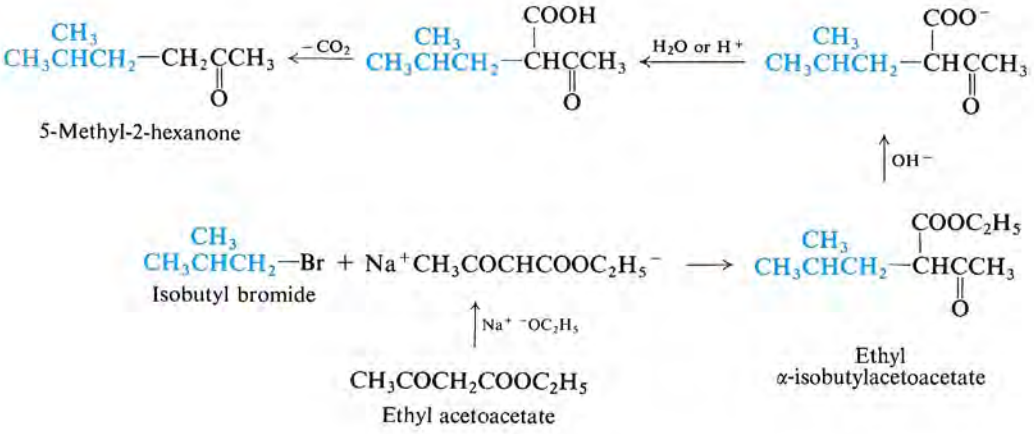
When hydrolyzed by dilute aqueous alkali (or by acid), these monoalkylacetoacetic or dialkylacetoacetic esters yield the corresponding acids, $CH_3COCHRCOOH$ or $CH_3COCRR'COOH$, which undergo decarboxylation to form ketones, CH_3COCH_2R or $CH_3COCHRR'$. This loss of carbon dioxide occurs

Acetoacetic ester synthesis of ketones

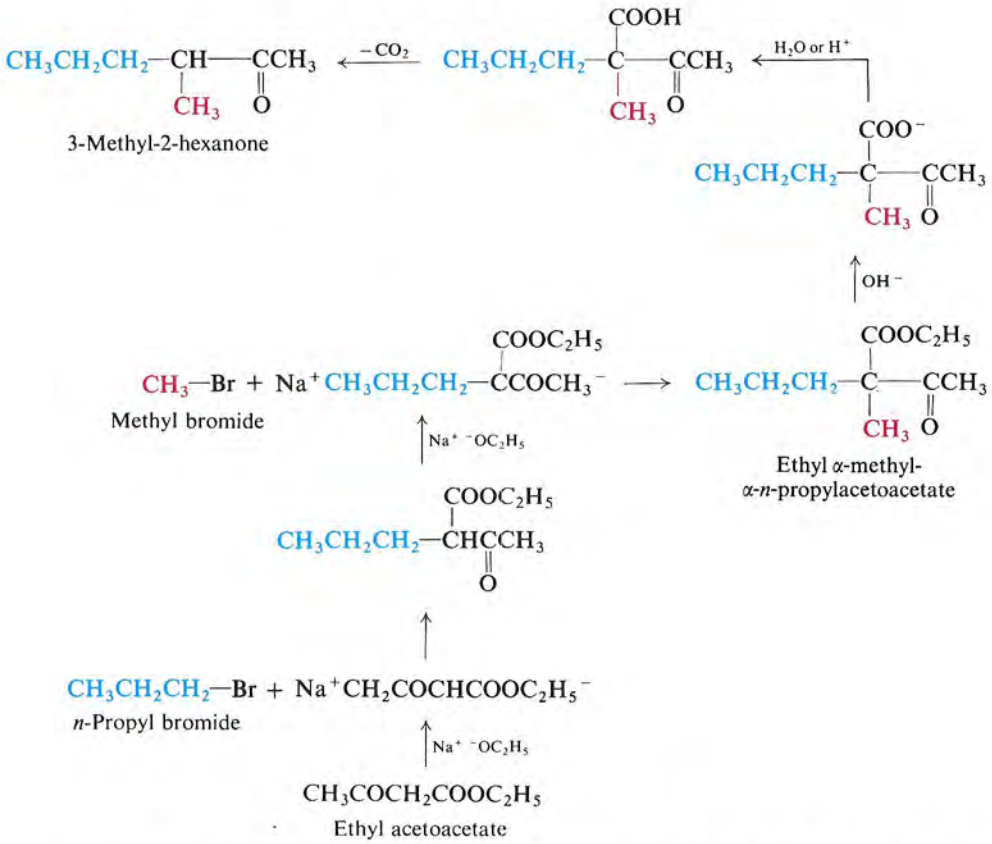


The acetoacetic ester synthesis of ketones yields an acetone molecule in which one or two hydrogens have been replaced by alkyl groups.

In planning an acetoacetic ester synthesis, as in planning a malonic ester synthesis, our problem is to select the proper alkyl halide or halides. To do this, we have only to look at the structure of the ketone we want. For example, 5-methyl-2-hexanone can be considered as acetone in which one hydrogen has been replaced by an isobutyl group. In order to prepare this ketone by the acetoacetic ester synthesis, we would have to use isobutyl bromide as the alkylating agent:



The isomeric ketone 3-methyl-2-hexanone can be considered as acetone in which one hydrogen has been replaced by a *n*-propyl group and a second hydrogen (on the same carbon) has been replaced by a methyl group; we must therefore use two alkyl halides, *n*-propyl bromide and methyl bromide:



Like the malonic ester synthesis, this synthesis, too, can be modified by changes in the base, solvent, and alkylating agent.

Problem 25.6 To what general class does the reaction between sodioacetoacetic ester and an alkyl halide belong? Predict the relative yields using primary, secondary, and tertiary halides. Can aryl halides be used?

Problem 25.7 (a) Predict the product of the acetoacetic ester synthesis in which ethyl bromoacetate (why not bromoacetic *acid*?) is used as the halide. To what general class of compounds does this product belong? (b) Predict the product of the acetoacetic ester synthesis in which benzoyl chloride is used as the halide; in which chloroacetone is used as the halide. To what general classes of compounds do these products belong?

Problem 25.8 Outline the synthesis of each of the following compounds from acetoacetic ester, benzene, and alcohols of four carbons or fewer:

(a)–(c) the isomeric ketones:
methyl *n*-butyl ketone (2-hexanone)
methyl isobutyl ketone (4-methyl-2-pentanone)
methyl *sec*-butyl ketone (3-methyl-2-pentanone)

(d) Why can the acetoacetic ester synthesis not be used for the preparation of methyl *tert*-butyl ketone?
(e) 2,4-pentanedione
(f) 2,5-hexanedione
(g) 1-phenyl-1,4-pentanedione

Problem 25.9 The best general preparation of **α-keto acids** is illustrated by the sequence:

$$\text{ethyl propionate} + \text{ethyl oxalate} \xrightarrow{NaOC_2H_5} B\,(C_9H_{14}O_5)$$

$$B + \text{dil. } H_2SO_4 \xrightarrow{\text{boil}} CO_2 + 2C_2H_5OH + CH_3CH_2\underset{\underset{O}{\|}}{C}COOH \text{ (α-ketobutyric acid)}$$

What familiar reactions are involved? What is the structure of B?

Problem 25.10 Outline the synthesis from simple esters of:
(a) α-ketoisocaproic acid
(b) α-keto-β-phenylpropionic acid
(c) α-ketoglutaric acid
(d) *leucine* (α-aminoisocaproic acid) (*Hint*: See Sec. 22.11.)
(e) *glutamic acid* (α-aminoglutaric acid)

25.4 Decarboxylation of β-keto acids and malonic acids

The acetoacetic ester synthesis thus depends on (a) the high acidity of the α-hydrogens of β-keto esters, and (b) the extreme ease with which β-keto acids undergo decarboxylation. These properties are exactly parallel to those on which the malonic ester synthesis depends.

We have seen that the higher acidity of the α-hydrogens is due to the ability of the keto group to help accommodate the negative charge of the acetoacetic ester anion. The ease of decarboxylation is, in part, due to *exactly the same factor*. (So, too, is the occurrence of the Claisen condensation, by which the acetoacetic ester is made in the first place.)

Decarboxylation of β-keto acids involves both the free acid and the carboxylate ion. Loss of carbon dioxide from the anion yields the carbanion I. This carbanion

$$CH_3-\underset{\underset{O}{\|}}{C}-CH_2-COO^- \longrightarrow CH_3-\underset{\underset{O^{\ominus}}{|}}{C}{=}CH_2 + CO_2$$

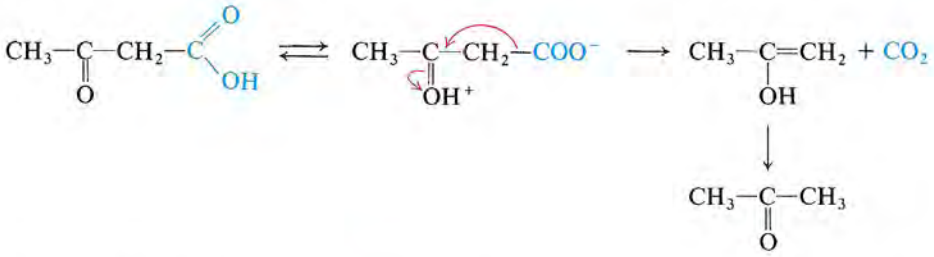
I

is formed faster than the simple carbanion ($R:^-$) that would be formed from a simple carboxylate ion ($RCOO^-$) because it is more stable. It is more stable, of course, due to the accommodation of the negative charge by the keto group.

Problem 25.11 Decarboxylation of malonic acid involves both the free acid and the monoanion, but not the doubly charged anion. (a) Account for the ease of decarboxylation of the monoanion. Which end loses carbon dioxide? (b) How do you account for the lack of reactivity of the doubly charged anion? (*Hint*: See Sec. 19.20.)

Problem 25.12 In contrast to most carboxylic acids (benzoic acid, say) 2,4,6-trinitrobenzoic acid is decarboxylated extremely easily: by simply boiling it in aqueous acid. How do you account for this?

Decarboxylation of free acetoacetic acid involves transfer of the acidic hydrogen to the keto group, either *prior to* (as shown here) or *simultaneously with*



loss of carbon dioxide. We are quite familiar with the function of protonation to reduce the basicity of a leaving group.

Problem 25.13 When dimethylacetoacetic acid is decarboxylated in the presence of iodine or bromine, there is obtained an iododimethylacetone or a bromodimethylacetone (3-halo-3-methyl-2-butanone), although under these conditions neither iodine nor bromine reacts significantly with the dimethylacetone. What bearing does this experiment have on the mechanism of decarboxylation?

Problem 25.14 Suggest a mechanism for the decarboxylation of free malonic acid.

Problem 25.15 Account for the comparative ease with which phenylpropiolic acid, $C_6H_5C{\equiv}CCOOH$, undergoes decarboxylation in alkaline solution.

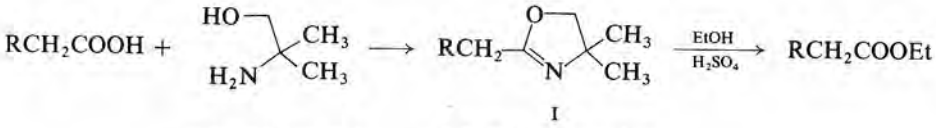
25.5 Direct and indirect alkylation of esters and ketones

By the malonic ester and acetoacetic ester we make α-substituted acids and α-substituted ketones. But why not do the job *directly*? Why not convert simple acids (or esters) and ketones into their carbanions, and allow these to react with alkyl halides? There are a number of obstacles: (a) self-condensation—aldol condensation, for example, of ketones; (b) polyalkylation; and (c) for unsymmetrical ketones, alkylation at *both* α-carbons, or at the wrong one. Consider self-condensation. A carbanion can be generated from, say, a simple ketone; but, instead of attacking a molecule of alkyl halide, the carbanion may attack the carbonyl carbon of a second ketone molecule. What is needed is a base–solvent combination that can convert the ketone *rapidly* and essentially *completely* into the carbanion before appreciable self-condensation can occur. Steps toward solving this problem have been taken, and there are available methods—so far, of limited applicability—for the direct alkylation of acids and ketones.

A tremendous amount of work has gone into the development of alternatives to direct alkylation. Another group is introduced temporarily to do one or more of these things: increase the acidity of the α-hydrogens, prevent self-condensation, and direct alkylation to a specific position. The malonic ester and acetoacetic ester syntheses are, of course, typical of this approach. In the acetoacetic ester synthesis, for example, the carbethoxy group, —COOEt, enhances the acidity of α-hydrogens, but only those on one particular α-carbon, so that alkylation will take place there. Then, when alkylation is over, the carbethoxy group is easily removed by hydrolysis and decarboxylation.

Synthesis of acids and esters via 2-oxazolines

Reaction of a carboxylic acid with 2-amino-2-methyl-1-propanol yields a heterocyclic compound called a *2-oxazoline* (I). From this compound the acid can be regenerated, in the form of its ethyl ester, by ethanolysis.

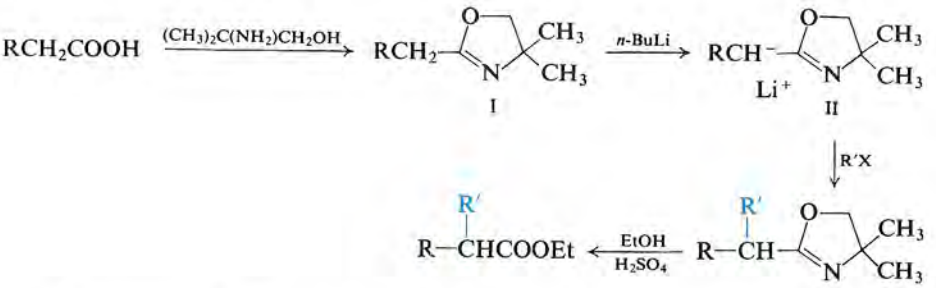


I

2-Amino-2-methyl 1-propanol

A 2-alkyl-4,4-dimethyl-2-oxazoline

Using this way to protect the carboxyl group, A. I. Meyers (Colorado State University) has recently opened an elegant route to alkylated acetic acids—or, by modification, to β-hydroxy esters.



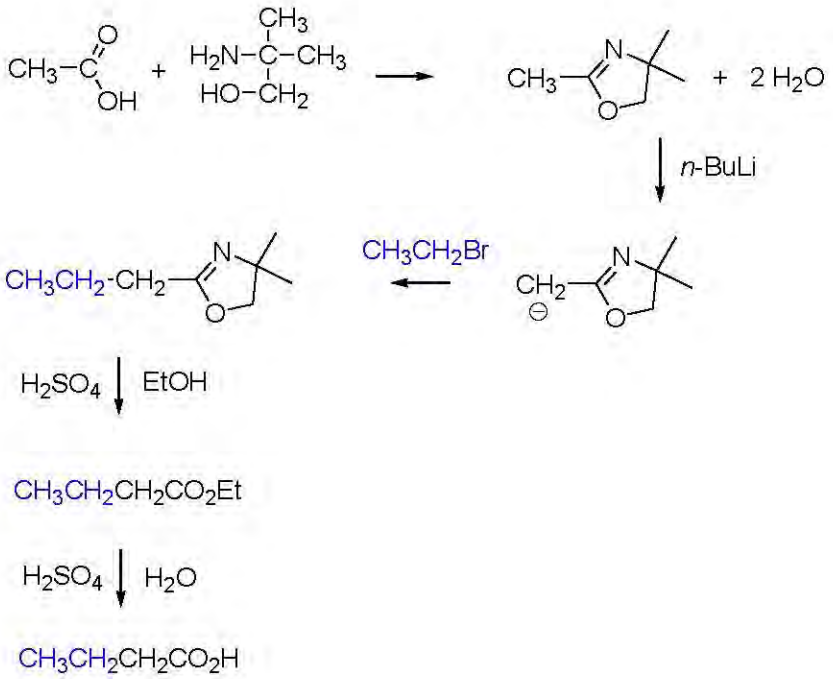
I II

Treatment of the 2-oxazoline with the strong base, *n*-butyllithium, yields the lithio derivative II. This, like sodiomalonic ester, can be alkylated and, if desired, re-alkylated—up to a total of *two* substituents on the α-carbon. Ethanolysis of the new 2-oxazoline yields the substituted ester.

The synthesis depends upon: (a) the ease of formation and hydrolysis of 2-oxazolines; (b) the fact that the α-hydrogens retain their acidity in the oxazoline (*Why*?); and (c) the inertness of the 2-oxazoline ring toward the lithio derivative. (The ring is inert toward the Grignard reagent as well, and can be used to protect the carboxyl group in a wide variety of syntheses.)

Problem 25.16 Using the Meyers oxazoline method, outline all steps in the synthesis of: (a) *n*-butyric acid from acetic acid; (b) isobutyric acid from acetic acid; (c) isobutyric acid from propionic acid; (d) β-phenylpropionic acid from acetic acid.

synthesis of butyric acid from acetic acid via 2-oxazoline method



Organoborane synthesis of acids and ketones

In the presence of base, alkylboranes react with bromoacetone to yield alkylacetones, and with ethyl bromoacetate to yield ethyl alkylacetates.

$$R_3B + BrCH_2COCH_3 \xrightarrow{base} R{-}CH_2COCH_3$$

Bromoacetone — An alkylacetone

$$R_3B + BrCH_2COOEt \xrightarrow{base} R{-}CH_2COOEt$$

Ethyl bromoacetate — An ethyl alkylacetate

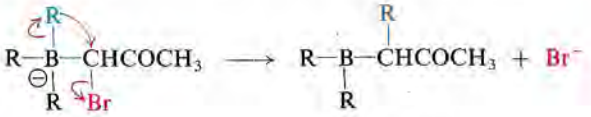
The following mechanism has been postulated, illustrated for reaction with bromoacetone. Base abstracts (1) a proton—one that is *alpha* both to the carbonyl group and to bromine—to give the carbanion I. Being a strong base, carbanion I

(1) $$:Base^- + CH_2BrCOCH_3 \rightleftharpoons {}^-CHBrCOCH_3 + H{:}Base$$

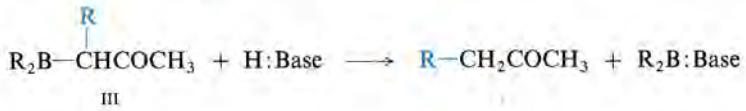
I

(2) $$R_3B + {}^-CHBrCOCH_3 \longrightarrow R_3\overset{\ominus}{B}{:}CHBrCOCH_3$$

I — II

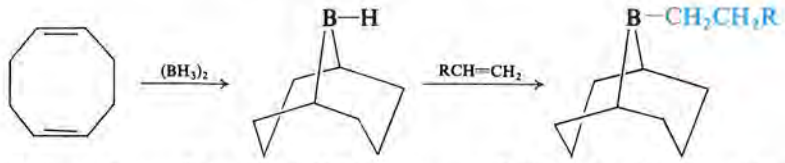
(3) 

II — III

(4) 

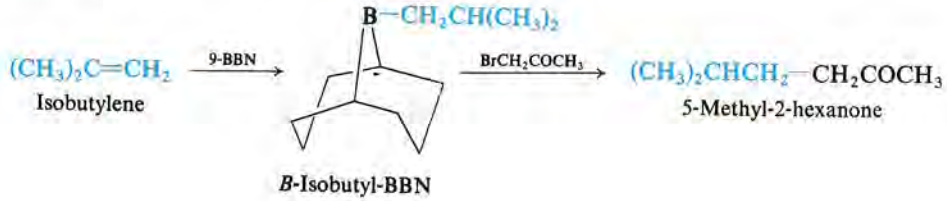
III

Consistently high yields depend on the proper selection of reagents. In general, the best base is the bulky potassium 2,6-di-*tert*-butylphenoxide. The best alkylating agent is *B*-alkyl-9-borabicyclo[3.3.1]nonane, or "*B*-alkyl-9-BBN", available via successive hydroborations of alkenes:

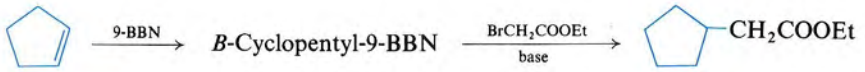


1,5-Cyclooctadiene — 9-Borabicyclo[3.3.1]nonane (9-BBN) *As dimer* — *B*-Alkyl-9-borabicyclo[3.3.1]nonane (*B*-Alkyl-9-BBN)

The overall synthesis thus amounts to the conversion of alkenes into ketones and esters. For example:



Isobutylene — *B*-Isobutyl-BBN — 5-Methyl-2-hexanone



Cyclopentene

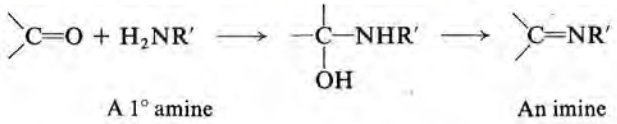
Ethyl cyclopentylacetate

Problem 25.19 Using 9-BBN plus any alkenes and unhalogenated acids or ketones, outline all steps in the synthesis of:

(a) 2-heptanone
(b) 4-methylpentanoic acid
(c) 4-methyl-2-hexanone
(d) 1-cyclohexyl-2-propanone
(e) ethyl (*trans*-2-methylcyclopentyl)acetate
(f) 1-phenyl-4-methyl-1-pentanone
(g) 1-cyclopentyl-3,3-dimethyl-2-butanone

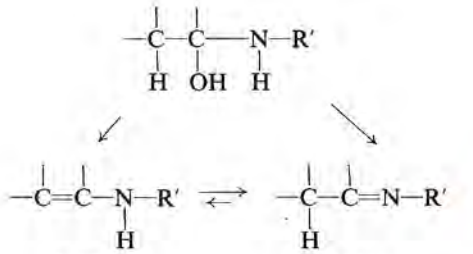
Alkylation of carbonyl compounds via enamines

As we might expect, amines react with carbonyl compounds by nucleophilic addition. If the amine is *primary*, the initial addition product undergoes dehydration (compare Sec. 18.11) to form a compound containing a carbon–nitrogen double



A 1° amine — An imine

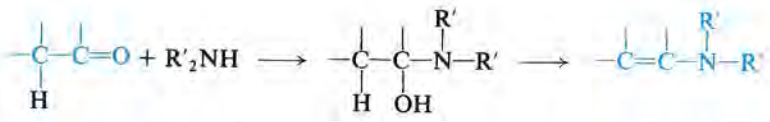
bond, an *imine*. Elimination occurs with this orientation even if the carbonyl compound contains an α-hydrogen: that is, the preferred product is the imine rather than the *enamine* (*ene* for the carbon–carbon double bond, *amine* for the amino group). If some enamine should be formed initially, it rapidly tautomerizes into the more stable imino form.



Enamine — Imine

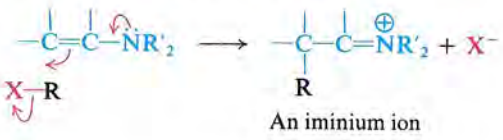
More stable form

Imine–enamine tautomerism



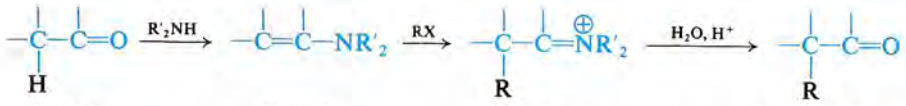
A 2° amine — An enamine

The usefulness of enamines stems from the fact that they contain *nucleophilic carbon*. The electrons responsible for this nucleophilicity are, in the final analysis, the (formally) unshared pair on nitrogen; but they are available for nucleophilic attack by carbon of the enamine. Thus, in alkylation:



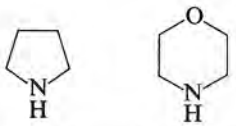
An iminium ion

The product of alkylation is an iminium ion, which is readily hydrolyzed to regenerate the carbonyl group. The overall process, then, is:



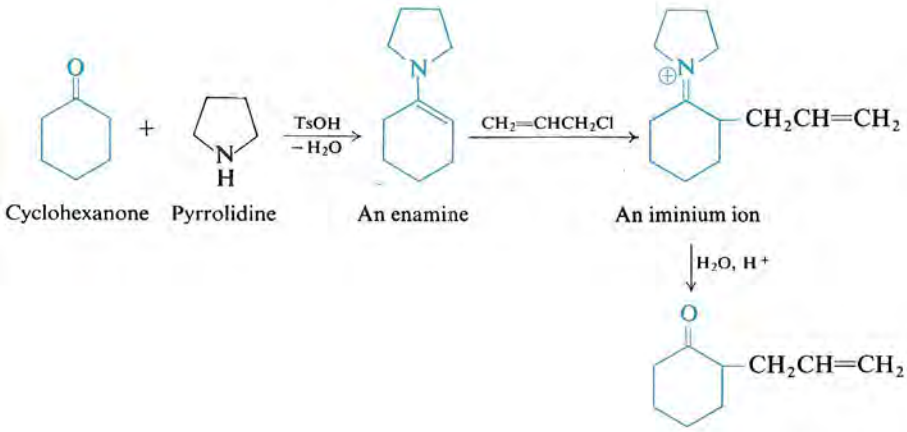
Ketone — Enamine — Iminium ion — Alkylated ketone

Commonly used secondary amines are the heterocyclic compounds *pyrrolidine* and *morpholine*:

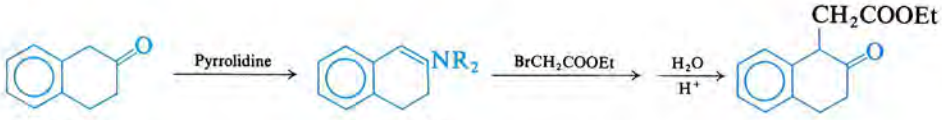


Pyrrolidine Morpholine

EXAMPLES

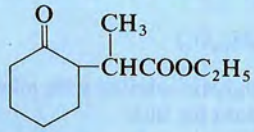
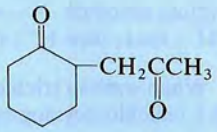


Cyclohexanone Pyrrolidine An enamine An iminium ion



β-Tetralone An enamine

Problem 25.20 Outline all steps in the preparation of each of the following by the enamine synthesis:

(a) 2-benzylcyclohexanone
(b) 2,2-dimethyl-4-pentenal
(c) 
(d) 
(e) 2-(2,4-dinitrophenyl)cyclohexanone
(f) 2,2-dimethyl-3-oxobutanal, $CH_3COC(CH_3)_2CHO$

Problem 25.21 Give structural formulas of compounds F–K.

(a) cyclopentanone + morpholine, then TsOH $\longrightarrow$ F ($C_9H_{15}ON$)
F + C_6H_5CHO, then H_2O, H^+ $\longrightarrow$ G ($C_{12}H_{12}O$)
(b) isobutyraldehyde + *tert*-butylamine $\longrightarrow$ H ($C_8H_{17}N$)
H + C_2H_5MgBr $\longrightarrow$ I ($C_8H_{16}NMgBr$) + J
I + $C_6H_5CH_2Cl$, then H_2O, H^+ $\longrightarrow$ K ($C_{11}H_{14}O$)

PROBLEMS

1. Outline the synthesis of each of the following from malonic ester and any other reagents:

(a) *n*-caproic acid
(b) isobutyric acid
(c) β-methylbutyric acid
(d) α,β-dimethylbutyric acid
(e) 2-ethylbutanoic acid
(f) dibenzylacetic acid
(g) α,β-dimethylsuccinic acid
(h) glutaric acid
(i) cyclobutanecarboxylic acid

2. Outline the synthesis of each of the following from acetoacetic ester and any other needed reagents. Do (j)–(m) after Problem 11, below.

(a) methyl ethyl ketone
(b) 3-ethyl-2-pentanone
(c) 3-ethyl-2-hexanone
(d) 5-methyl-2-heptanone
(e) 3,6-dimethyl-2-heptanone
(f) 4-oxo-2-methylpentanoic acid
(g) γ-hydroxy-*n*-valeric acid
(h) 3-methyl-2-hexanol
(i) 2,5-dimethylheptane
(j) β-methylcaproic acid
(k) β-methylbutyric acid
(l) methylsuccinic acid
(m) 2,5-hexanediol

3. What product would you expect from the hydrolysis by dilute alkali of 2-carbethoxycyclopentanone (see Problem 21.25, p. 815)? Suggest a method of synthesis of 2-methylcyclopentanone.

4. Give structures of compounds A through J:

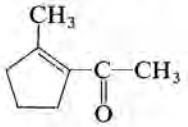
(a) 1,3-dibromopropane + 2 mol sodiomalonic ester $\longrightarrow$ A ($C_{17}H_{28}O_8$)
A + 2 mol sodium ethoxide; then CH_2I_2 $\longrightarrow$ B ($C_{18}H_{28}O_8$)
B + OH^-, heat; then H^+; then heat $\longrightarrow$ C ($C_8H_{12}O_4$)
(b) ethylene bromide + 2 mol sodiomalonic ester $\longrightarrow$ D ($C_{16}H_{26}O_8$)
D + 2 mol sodium ethoxide; then 1 mol ethylene bromide $\longrightarrow$ E ($C_{18}H_{28}O_8$)
E + OH^-, heat; then H^+; then heat $\longrightarrow$ F ($C_8H_{12}O_4$)
(c) 2 mol sodiomalonic ester + I_2 $\longrightarrow$ G ($C_{14}H_{22}O_8$) + 2NaI
G + OH^-, heat; then H^+; then heat $\longrightarrow$ H ($C_4H_6O_4$)
(d) D + 2 mol sodium ethoxide; then I_2 $\longrightarrow$ I ($C_{16}H_{24}O_8$)
I + OH^-, heat; then H^+; then heat $\longrightarrow$ J ($C_6H_8O_4$)
(e) Suggest a possible synthesis for 1,3-cyclopentanedicarboxylic acid; for 1,2-cyclopentanedicarboxylic acid; for 1,1-cyclopentanedicarboxylic acid.

5. Give structures of compounds K through O:

allyl bromide + Mg $\longrightarrow$ K (C_6H_{10})
K + HBr $\longrightarrow$ L ($C_6H_{12}Br_2$)
sodiomalonic ester + excess L $\longrightarrow$ M ($C_{13}H_{23}O_4Br$)
M + sodium ethoxide $\longrightarrow$ N ($C_{13}H_{22}O_4$)
N + OH^-, heat; then H^+; then heat $\longrightarrow$ O ($C_8H_{14}O_2$)

6. When sodium trichloroacetate is heated in diglyme solution with alkenes, there are formed 1,1-dichlorocyclopropanes. How do you account for this?

7. (a) How could you synthesize 2,7-octanedione? (*Hint*: See Problem 25.2, p. 927.) (b) Actually, the expected ketone reacts further to give



How does this last reaction occur? To what general types does it belong? (c) How could you synthesize 2,6-heptanedione? (d) What would happen to this ketone under the conditions of (b)?

8. Outline all steps in a possible synthesis of each of the following from simple esters:

(a) 1,2-cyclopentanedione (*Hint*: See Problem 21.28, p. 816.)
(b) $CH_3CH_2CH_2COCOOC_2H_5$ (*Hint*: See Problem 25.9, p. 930.)

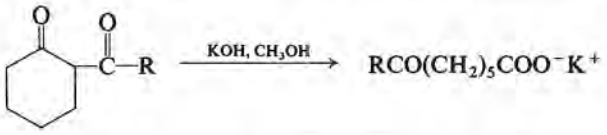
9. Outline the synthesis from readily available compounds of the following hypnotics (see Sec. 20.23):

(a) 5,5-diethylbarbituric acid (Barbital, Veronal; long-acting)
(b) 5-allyl-5-(2-pentyl)barbituric acid (Seconal; short-acting)
(c) 5-ethyl-5-isopentylbarbituric acid (Amytal; intermediate length of action)

10. (a) Contrast the structures of barbituric acid and Veronal (5,5-diethylbarbituric acid). (b) Account for the appreciable acidity ($K_a = 10^{-8}$) of Veronal.

11. When treated with *concentrated* alkali, acetoacetic ester is converted into two moles of sodium acetate. (a) Outline all steps in a likely mechanism for this reaction. (*Hint*: See Secs. 21.11 and 8.26.) (b) Substituted acetoacetic esters also undergo this reaction. Outline the steps in a general synthetic route from acetoacetic ester to carboxylic acids.(c) Outline the steps in the synthesis of 2-hexanone via acetoacetic ester. What acids will be formed as by-products? Outline a procedure for purification of the desired ketone. (Remember that the alkylation is carried out in alcohol; that NaBr is formed; that aqueous base is used for hydrolysis; and that ethyl alcohol is a product of the hydrolysis.)

12. (a) Suggest a mechanism for the alkaline cleavage of β-diketones, as, for example:



(b) Starting from cyclohexanone, and using any other needed reagents, outline all steps in a possible synthesis of 7-phenylheptanoic acid. (c) Of pentadecanedioic acid, $HOOC(CH_2)_{13}COOH$.

13. Give structures of compounds P through S:

heptanal (heptaldehyde) + ethyl bromoacetate + Zn, then H_2O $\longrightarrow$ P ($C_{11}H_{22}O_3$)
P + CrO_3 in glacial acetic acid $\longrightarrow$ Q ($C_{11}H_{20}O_3$)
Q + sodium ethoxide; then benzyl chloride $\longrightarrow$ R ($C_{18}H_{26}O_3$)
R + OH^-, heat; then H^+, warm $\longrightarrow$ S ($C_{15}H_{22}O$)

Useful information: In what is called the *Reformatsky* reaction, organozinc compounds act like (somewhat unreactive) Grignard reagents.

14. Treatment of 1,5-cyclooctadiene with diborane gives a material, T, which is oxidized by alkaline H_2O_2 to a mixture of 72% *cis*-1,5-cyclooctanediol and 28% *cis*-1,4-cyclooctanediol. If T is refluxed for an hour in THF solution (or simply distilled), there is obtained a white crystalline solid, U, which is oxidized to 99%-pure *cis*-1,5-cyclooctanediol.

(a) What is T? What is U? (b) Account for the conversion of T into U.

15. On treatment with concentrated KOH, 2,6-dichlorobenzaldehyde is converted into 1,3-dichlorobenzene and potassium formate. The kinetics shows that the aldehyde and two moles of hydroxide ion are in equilibrium with a reactive intermediate that (ultimately) yields product. (a) Outline a likely mechanism that is consistent with these facts. (*Hint*: See Sec. 18.13.) (b) How do you account for the difference in behavior between this aldehyde and most aromatic aldehydes under these conditions?

16. Give structural formulas of compounds V and W, and tell *exactly* how each is formed:

γ-butyrolactone + CH_3ONa $\longrightarrow$ V ($C_8H_{10}O_3$)
V + conc. HCl $\longrightarrow$ W ($C_7H_{12}OCl_2$)
W + aq. NaOH $\longrightarrow$ dicyclopropyl ketone

17. The structure of *nerolidol*, $C_{15}H_{26}O$, a terpene found in oil of neroli, was established by the following synthesis:

geranyl chloride (RCl) + sodioacetoacetic ester $\longrightarrow$ X ($RC_6H_9O_3$)
X + $Ba(OH)_2$; then H^+, warm $\longrightarrow$ Y (RC_3H_5O)
Y + NaC≡CH; then H_2O $\longrightarrow$ Z (RC_5H_7O)
Z $\xrightarrow{\text{reduction}}$ AA (RC_5H_9O), nerolidol

(a) Give the structure of nerolidol, using R for the geranyl group.
(b) Referring to Problem 29, p. 647, what is the complete structure of nerolidol?

18. The structure of *menthone*, $C_{10}H_{18}O$, a terpene found in peppermint oil, was first established by synthesis in the following way:

ethyl β-methylpimelate + sodium ethoxide, then H_2O $\longrightarrow$ BB ($C_{10}H_{16}O_3$)
BB + sodium ethoxide; then isopropyl iodide $\longrightarrow$ CC ($C_{13}H_{22}O_3$)
CC + OH^-, heat; then H^+; then heat $\longrightarrow$ menthone

(a) What structures for menthone are consistent with this synthesis? (b) On the basis of the isoprene rule (Sec. 11.25) which structure is the more likely? (c) On vigorous reduction menthone yields *p-menthane*, 4-isopropyl-1-methylcyclohexane. Now what structure or structures are most likely for menthone?

19. The structure of *camphoronic acid* (a degradation product of the terpene camphor) was established by the following synthesis:

sodioacetoacetic ester + CH_3I $\longrightarrow$ DD $\xrightarrow{NaOC_2H_5}$ $\xrightarrow{CH_3I}$ EE ($C_8H_{14}O_3$)
EE + ethyl bromoacetate + Zn; then H_2O $\longrightarrow$ FF ($C_{12}H_{22}O_5$)
FF + PCl_5, then KCN $\longrightarrow$ GG ($C_{13}H_{21}O_4N$)
GG + H_2O, H^+, heat $\longrightarrow$ camphoronic acid ($C_9H_{14}O_6$)

What is the structure of camphoronic acid?

20. Two of the oxidation products of the terpene α-terpineol are *terebic acid* and *terpenylic acid*. Their structures were first established by the following synthesis:

ethyl chloroacetate + sodioacetoacetic ester $\longrightarrow$ HH ($C_{10}H_{16}O_5$)
HH + 1 mol CH_3MgI; then H_2O $\longrightarrow$ II ($C_{11}H_{20}O_5$)
II + OH^-, H_2O, heat; then H^+ $\longrightarrow$ [JJ ($C_7H_{12}O_5$)] $\longrightarrow$ terebic acid ($C_7H_{10}O_4$)
HH + sodium ethoxide; then ethyl chloroacetate $\longrightarrow$ KK ($C_{14}H_{22}O_7$)
KK + OH^-; then H^+, warm $\longrightarrow$ LL ($C_7H_{10}O_5$)
LL + ethyl alcohol, H^+ $\longrightarrow$ MM ($C_{11}H_{18}O_5$)
MM + 1 mol CH_3MgI; then H_2O $\longrightarrow$ NN ($C_{12}H_{22}O_5$)
NN + OH^-, H_2O, heat; then H^+ $\longrightarrow$ [OO ($C_8H_{14}O_5$)] $\longrightarrow$
terpenylic acid ($C_8H_{12}O_4$)

What is the structure of terebic acid? Of terpenylic acid?

21. (a) Give structural formulas of compounds PP and QQ.

Oxazoline I (p. 932, R = H) + *n*-BuLi, then $CH_3(CH_2)_5CHO$ $\longrightarrow$ PP
PP + EtOH, H_2SO_4 $\longrightarrow$ QQ ($C_{11}H_{22}O_3$)

(b) Outline all steps in the synthesis of ethyl 3-(*n*-propyl)-3-hydroxyhexanoate. (c) Of ethyl 2-ethyl-3-phenyl-3-hydroxypropanoate.