

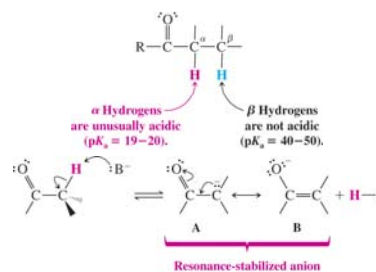
Chapter 18

Aldehydes and Ketones

Reaction at the α -carbon of carbonyl compounds

◆ The Acidity of the α Hydrogens of Carbonyl Compounds: Enolate Anions

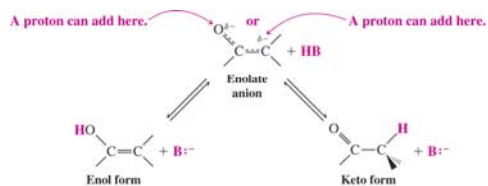
→ Hydrogens on carbons α to carbonyls are unusually acidic
 ↳ The resulting anion is stabilized by resonance to the carbonyl



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The enolate anion can be protonated at the carbon or the oxygen

→ The resultant enol and keto forms of the carbonyl are formed reversibly and are interconvertible

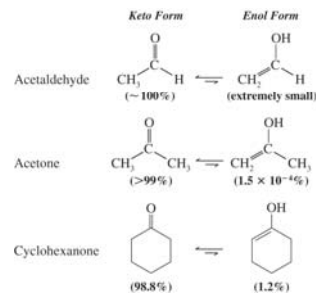


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◆ Keto and Enol Tautomers

→ Enol-keto tautomers are constitutional isomers that are easily interconverted by a trace of acid or base

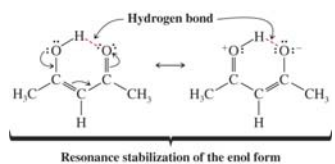
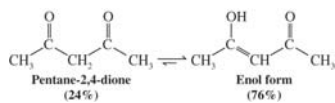
↳ Most aldehydes and ketones exist primarily in the keto form because of the greater strength of the carbon-oxygen double bond relative to the carbon-carbon double bond



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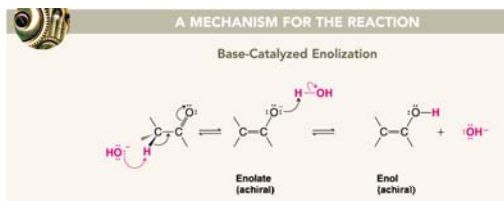
→ β -Dicarbonyl compounds exist primarily in the enol form

‡ The enol is more stable because it has a conjugated π system and because of stabilization of the enol through hydrogen bonding

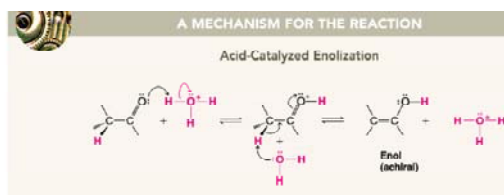


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Mechanism for Base- and Acid-catalyzed enolization



First – abstraction of the β -hydrogen

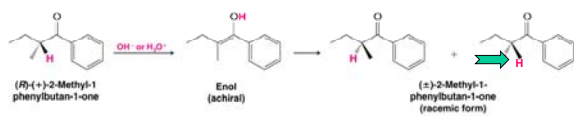


First – protonation of the oxygen from the carbonyl group

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Reactions via Enols and enolates - Racemization

Consequences of the keto-enol equilibration is the racemization of the chiral carbonyl compounds into racemic mixture in the basic or acidic conditions since enols are achiral intermediates

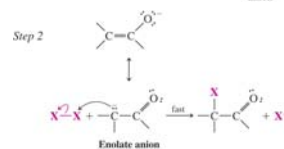
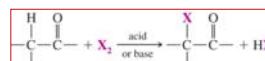


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• Halogenation of Ketones

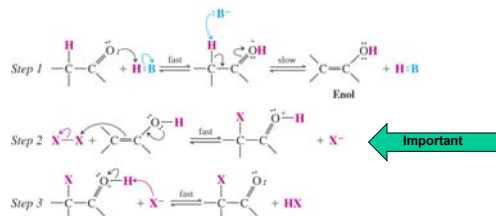
→ Ketones can be halogenated at the α position in the presence of acid or base and X_2

‡ Base-promoted halogenation occurs via an enolate



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Acid-catalyzed halogenation proceeds via the enol

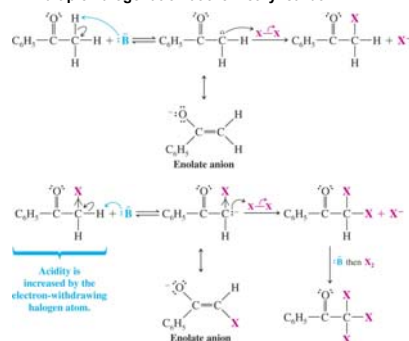


Overall effect α -substitution:
Replacement of proton with electrophile

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Haloform Reaction

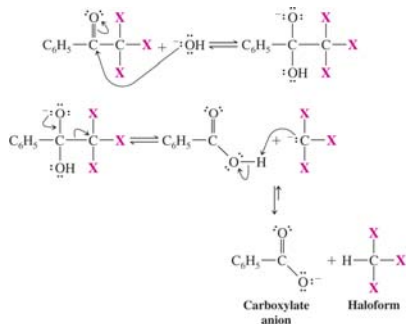
Reaction of methyl ketones with X_2 in the presence of base results in multiple halogenation at the methyl carbon



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When methyl ketones react with X_2 in aqueous hydroxide the reaction gives a carboxylate anion (carboxylic acids) and a haloform (CX_3H)

The trihalomethyl anion is a relatively good leaving group because the negative charge is stabilized by the three halogen atoms

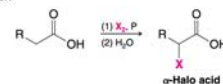


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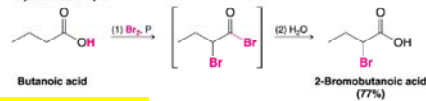
α -Halo Carboxylic Acids: The Hell-Volhard-Zelinski reaction

Carboxylic acids with α -hydrogens react with bromine or chlorine to give α -halo carboxylic acids.

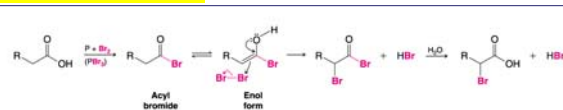
General Reaction



Specific Example

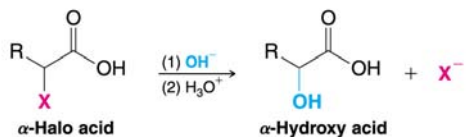


How does the reaction occur?

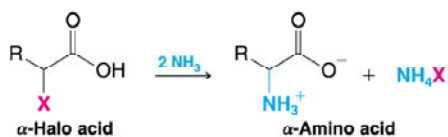


• α -Halo Carboxylic Acids: Synthetic applications

Conversion to α -Hydroxy Acids

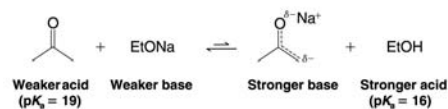


Conversion to α -Amino Acids

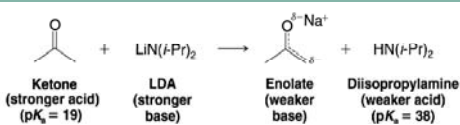


Formation of Lithium Enolates

→ Enolates can be conveniently generated by treatment of ketones with strong bases such as LDA

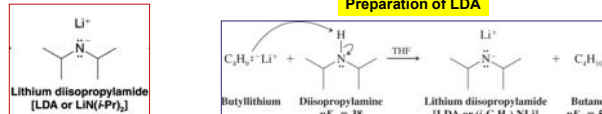


Since base employed is a weaker base than the enolate, this is not a very good approach



This is a good method since base employed is a stronger base than the enolate.

Preparation of LDA



Regioselective Formation of Enolate Anions

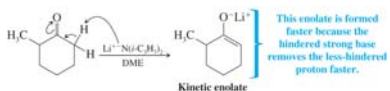
→ Unsymmetrical ketones can form two different enolates
 → The **thermodynamic enolate** is the most stable enolate i.e. the one with the more highly substituted double bond

‡ A weak base favors the thermodynamic enolate because an equilibrium between the enolates is established



→ The **kinetic enolate** is the enolate formed fastest and it usually is the enolate with the least substituted double bond

‡ A strong, sterically hindered base such as lithium diisopropyl amide favors formation of the kinetic enolate

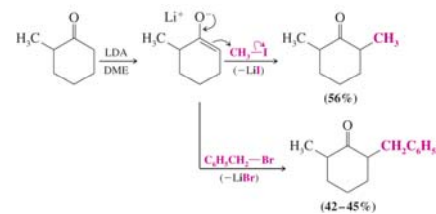


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• Direct Alkylation of Ketones via Lithium Enolates

→ Enolates can also be alkylated with primary alkyl, benzylic and allylic halides via an S_N2 reaction

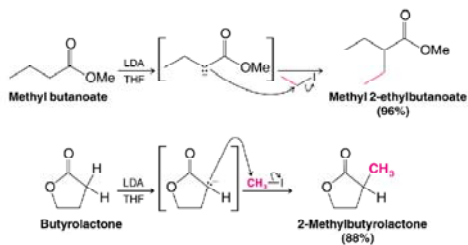
‡ Unsymmetrical ketones can be alkylated at the least substituted position if LDA is used to form the kinetic enolate



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• Direct Alkylation of Esters

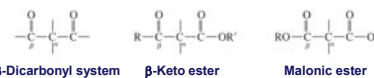
→ Enolates generated from esters (α -carbanions) can also be alkylated with **primary alkyl halides** via an S_N2 reaction



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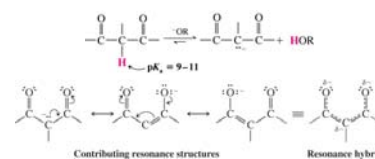
Enolates of β -Dicarbonyl compounds

→ β -Dicarbonyl compounds have two carbonyl groups separated by a carbon



→ Protons on the α -carbon of β -dicarbonyl compounds are acidic ($pK_a = 9-10$).

→ Recall that Protons for Ketones on the α -carbon have $pK_a = 18-20$
 This unusually low acidity for organic compounds can be explained by resonance stabilization of the corresponding enolate by two carbonyl groups



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Acidity of organic compounds (pK_a 's) (Page 111)

◆ Alkanes and alkenes R-H	45 (40-50)
◆ Terminal alkynes $\text{RC}\equiv\text{CH}$	25
◆ α -H of carbonyls (-CO-CH)	20
◆ Alcohols ROH	16 ($3^\circ = 18$)
◆ β -dicarbonyls $\text{RCO-CH}_2\text{-COR}$	10
◆ Phenol $\text{C}_6\text{H}_5\text{OH}$	10
◆ Carboxylic acids RCOOH	5

Comparisons: water = 15.7, NH_3 and H_2 about 35

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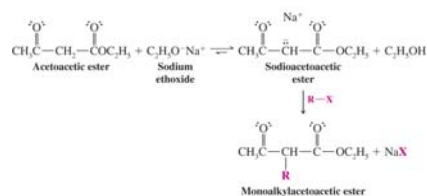
The Acetoacetic Ester Synthesis: Synthesis of Methyl Ketones (Substituted Acetones)

• Alkylation

→ Alkylation of the enolate derived from acetoacetic ester is called the acetoacetic ester synthesis

↳ This is an S_N2 reaction with the ethyl acetoacetate enolate acting as the nucleophile

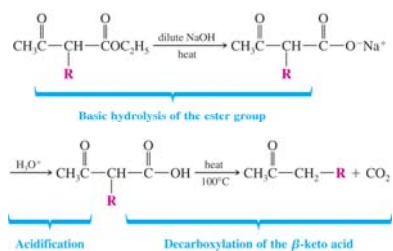
↳ Please note that contrary to ketones the sodium ethoxide is a sufficient base to generate enolates from β -Dicarbonyl compounds



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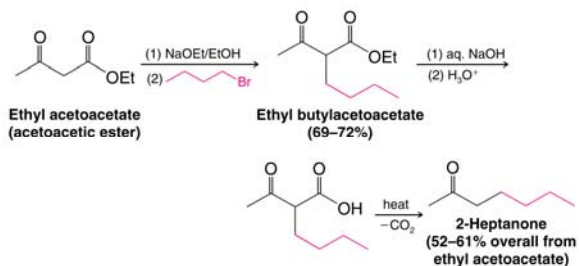
→ Hydrolysis of the ester and heating of the resultant β -ketoacid causes decarboxylation

⚡ The product is a substituted acetone derivative (methyl ketones)



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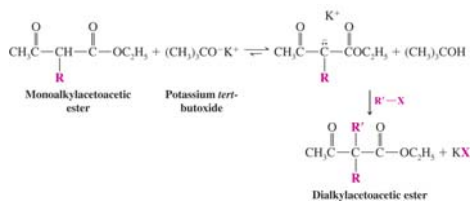
Specific example of the application of ethyl acetoacetate towards synthesis of monosubstituted acetone (methyl ketones)



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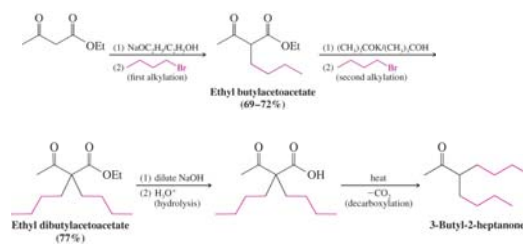
→ A second alkylation can be performed

⚡ A stronger base such as potassium *tert*-butoxide must be used to deprotonate the monoalkyl ester

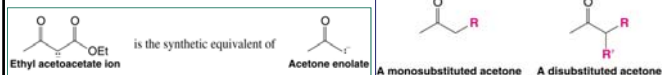


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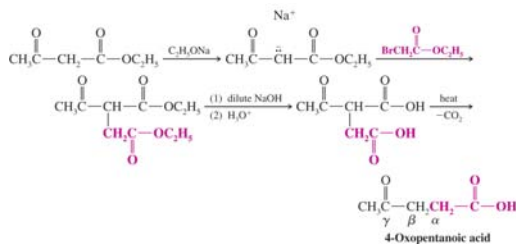
→ Example: Application of Acetoacetic ester towards synthesis of the α -(di)substituted methyl ketones (acetones)



Home take message



→ If α -halo esters are used to alkylate the acetoacetic ester enolate, γ -keto acids are obtained
(see review Problem 18.8)

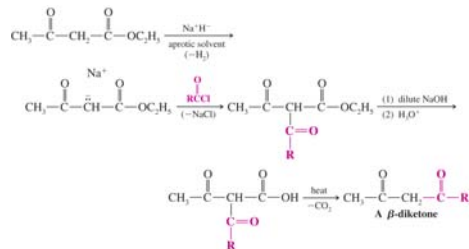


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● Acylation of Ethyl Acetoacetate anion

→ Acetoacetic ester anion (enolate) can also be acylated with acyl halides or anhydrides to produce β -diketones

! The reaction is carried out in aprotic solvents such as DMF or DMSO because these will not destroy the acylating reagents

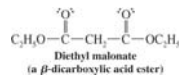


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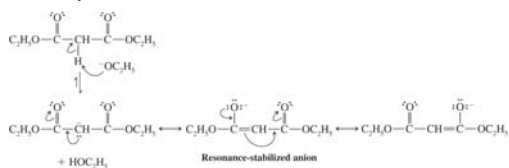
The Malonic Ester Synthesis: Synthesis of Substituted Acetic Acids

→ (1) Alkylation of diethylmalonate, (2) hydrolysis of the diester to the β -dicarboxylic acid, and (3) decarboxylation steps can be used to synthesize mono- and disubstituted acetic acids

! The mechanism is analogous to that for the acetoacetic ester synthesis



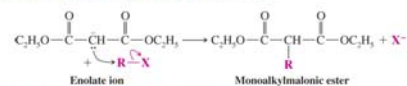
→ In step 1 the stabilized anion is formed



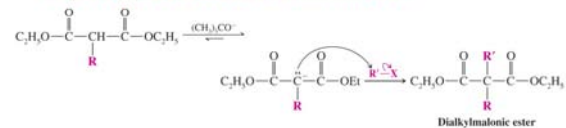
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→ In step 2 the anion is mono- or dialkylated using S_N2 reactions with primary alkyl halides

Step 2 This enolate anion can be alkylated in an S_N2 reaction,

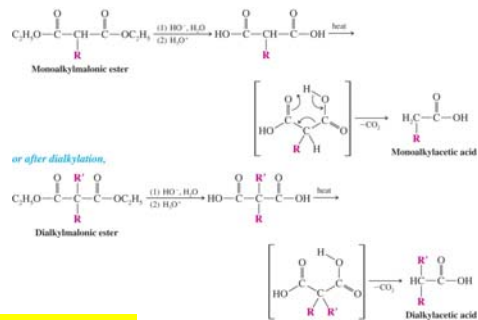


and the product can be alkylated again if our synthesis requires it:

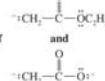
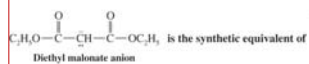


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→ In step 3 the mono- or dialkylated product is hydrolyzed and decarboxylated

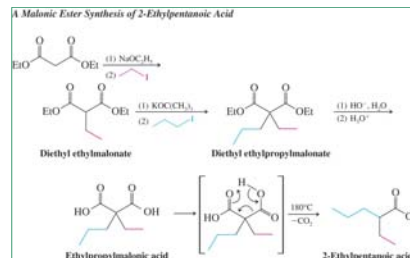
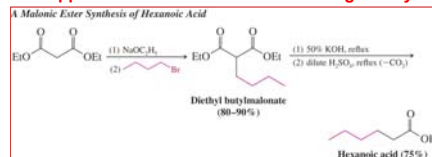


Home take message



Diethyl malonate anion is the synthetic equivalent of acetic acid dianion

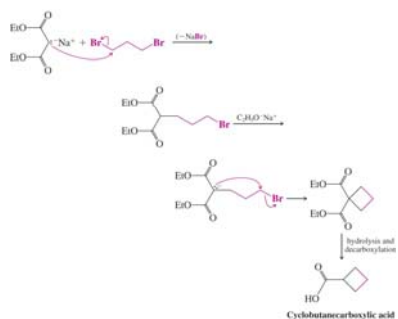
The Application of the Malonic Ester in Organic Synthesis



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→ Malonic Ester can be applied towards synthesis of 3-, 4-, 5-, and 6-membered rings.

For example terminal dihalides can react to form rings by alkylation of one molar equivalent of malonate. The resulting haloalkylmalonic ester can undergo internal alkylation via S_N2 reaction

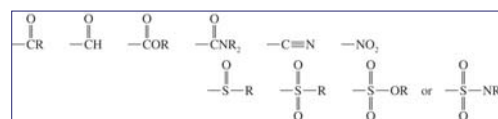
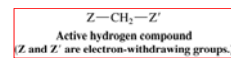


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♦ Reactions of Other Active Hydrogen Compounds

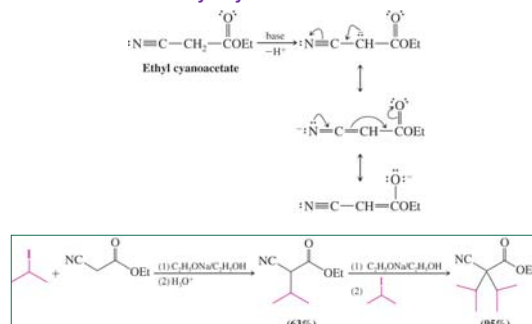
→ Compounds in which the hydrogen atoms of a methylene ($-CH_2-$) group are made acidic by two attached electron-withdrawing groups are called *active hydrogen compounds* or *active methylene compounds*

→ A variety of electron-withdrawing groups can produce enhanced α hydrogen acidity



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→ For Example deprotonation of ethyl cyanoacetate forms a resonance-stabilized anion, which can then undergo alkylation even with secondary alkyl halides

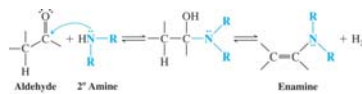


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◆ Synthesis of Enamines: Stork Enamine Reactions

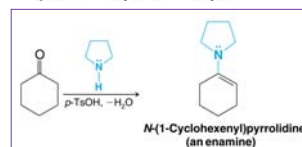
→ Aldehydes and ketones react with secondary amines to form enamines (see Section 16.8C)

- ‡ The reaction is catalyzed by acid
- ‡ Removal of water drives enamine formation to completion



Lack of hydrogen on nitrogen atom excludes formation of imine and therefore enamine is formed

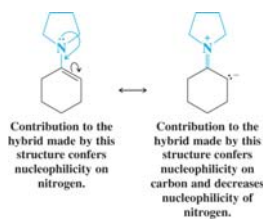
Cyclic amines are often used



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→ Enamines have a nucleophilic carbon and are the equivalent of ketone and aldehyde enolates

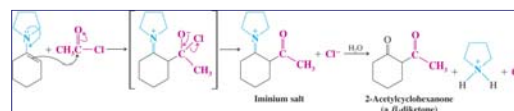
‡ The nitrogen of enamines is also nucleophilic



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→ Enamines can be acylated and alkylated

- ‡ The iminium intermediate is hydrolyzed when water is added
- C-Acylation leads to β -diketones



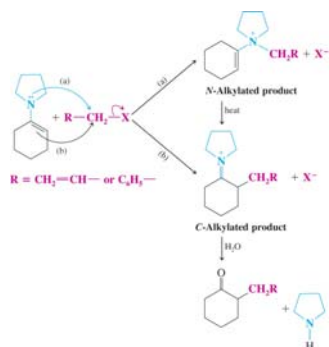
‡ N-acylated products can be formed, but they are unstable and act as acylating agents themselves (intramolecular acylation!)



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→ Alkylation of enamines can lead to some *N*-alkylation

Similarly to the *N*-acylated product discussed on the previous slide, the *N*-alkylated product can also be converted to the *C*-alkylated product by heating



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