Syntheses with Acetoacetaldehyde

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Acetoacetaldehyde

Free acetoacetaldehyde is as unstable as free acetoacetic acid. The compound was prepared first by Boileau (1) from sodium formylacetone with acetic anhydride in ether, or better, using less than an equivalent of chloroacetic acid (about a 40% yield). A colorless liquid (b.p. 30°/24 mm), having a camphorlike odor, it changes to triacetylbenzene on standing. The violet coloration with FeCl₃ is evidence for the enolization (1) which takes place at the aldehyde group as revealed by the IR spectrum.

Bokadia and Deshapande (2) furnished the chemical proof that the aldehyde group is enolized in α-formylketones by the reaction with phenyl isocyanate:

$$\text{C}_6\text{H}_{11}-\text{CO-CH=CHOH} \rightarrow \text{C}_6\text{H}_{11}-\text{CO-CH=CH-O-C=NH}_2\text{H}_3$$

An α-substituted derivative of the free acetoacetaldehyde was obtained in 17% yield by S. Hünig and O. Boes (3).

$$\text{CH}_3-\text{CO-CH=CHONa} + \text{O}_2\text{N-C}_6\text{H}_4-\text{N}_2\text{BF}_4 \rightarrow \text{O}_2\text{N-C}_6\text{H}_4-\text{NH-N=C-CO-CH}_3$$

Noteworthy is the formation of 2,2-dimethyl-3-oxo-1-butanal, \(\text{CH}_3\text{COC(CH}_3)_2\text{CHO}\), by the epoxidation of mesityl oxide and the isomerization of the epoxide with BF₃-ether in benzene (4). It was not possible to isolate the aldehyde by distillation, but the bis(p-nitrophenyl-hydrazone) was obtained in 58% yield.

Synthesis of Derivatives

SODIUM FORMYLACETONE (II)

Claisen (5) was the first to obtain the sodium salt of acetoacetaldehyde by the ester condensation of acetone and ethyl formate in the presence of sodium ethoxide in absolute ether:

$$\text{CH}_3-\text{CO-CH}_3 + \text{HCOOC}_2\text{H}_4 + \text{NaOC}_2\text{H}_4 \rightarrow \text{CH}_3-\text{CO-CH=CHONa} + 2 \text{C}_2\text{H}_5\text{OH}.$$
**TABLE 1**

**SUMMARY OF DERIVATIVES AND INTERMEDIATES OF ACETOACETALDEHYDE**

<table>
<thead>
<tr>
<th>Formula*</th>
<th>No.</th>
<th>Example</th>
<th>B.p. °C/mm</th>
<th>$n_\text{D}$</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH$_3$CXXCH$_2$CHX$_2$</td>
<td>I</td>
<td>CH$_3$COCH$_2$CH(OCH$_3$)$_2$ Acetoacetaldehyde dimethyl acetal; 3-ketobutyraldehyde dimethyl acetal; 4,4-dimethoxy-2-butanone</td>
<td>70-73°/20</td>
<td>1.4139</td>
<td>Commercial product</td>
</tr>
<tr>
<td>CH$_3$CXCH=CHX</td>
<td>II</td>
<td>CH$_3$COCH=CHOHNa Sodium formylacetone</td>
<td>—</td>
<td>—</td>
<td>Laboratory preparation</td>
</tr>
<tr>
<td>III</td>
<td>CH$_3$COCH=CHCl /3-Chlorovinyl methyl ketone; 1-Chloro-1-buten-3-one</td>
<td>42-43°/20</td>
<td>—</td>
<td>Laboratory preparation</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>CH$_3$COCH=CHOCH$_3$ 1-Methoxy-1-buten-3-one</td>
<td>172°</td>
<td>1.4699</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>CH$_3$C=CHCH(OCH$_3$)$_2$</td>
<td>V</td>
<td>CH$_3$C(OC$_3$)$_2$=CHCH(OC$_3$)$_2$ β-Methoxycrotonaldehyde dimethyl acetal</td>
<td>65°/19</td>
<td>1.4295</td>
<td>—</td>
</tr>
<tr>
<td>CH$_3$C≡CCHX$_2$</td>
<td>VI</td>
<td>CH$_3$C≡CCH(OC$_3$)$_2$ 2-Butynal dimethyl acetal</td>
<td>53°/15</td>
<td>1.4278</td>
<td>—</td>
</tr>
<tr>
<td>HC≡CCX$_2$CH$_3$</td>
<td>VII</td>
<td>HC≡CCOOCH$_3$ 1-Butyn-3-one</td>
<td>83.5-84.5°/752</td>
<td>1.4070</td>
<td>—</td>
</tr>
<tr>
<td>HC≡CCH≡CHX</td>
<td>VIII</td>
<td>HC≡CCH=CHOCH$_3$ 1-Methoxy-1-buten-3-yne</td>
<td>122°</td>
<td>1.475</td>
<td>Technical grade</td>
</tr>
</tbody>
</table>

* $X_2 = \angle O$; $X = ONa, OR, Cl, CN, NR_2$. 

WALTER FRANKE, RICHARD KRAFT, AND KURT KOSSWIG
From acetone, methyl formate, and sodium methoxide the sodium salt was obtained in 80–90% yield (6–8).

A flask, evacuated and then filled with nitrogen, is charged with 3.27 gm of alcohol-free sodium methoxide, 4.56 gm of ethyl formate, 3.58 gm of anhydrous acetone, and 150 ml of anhydrous ether. The light yellow reaction mixture is shaken for 10 min, then is allowed to stand at room temperature for 15 hr, care being taken to exclude air from the flask. When the supernatant is suctioned off with a filter stick from the powder-like precipitate, the latter is washed with ether and then dried over potassium hydroxide in a vacuum desiccator. Yield of sodium formylacetone: 6.03 gm (6). The substance can be stored for a long time in a well-stoppered flask.

**β-Chlorovinyl Methyl Ketone (III) (1-Chloro-1-butene-3-one)**

β-Chlorovinyl methyl ketone is obtained in 50 to 80% yield from acetylene and acetyl chloride with AlCl₃ in an inert solvent (9–13).

An interesting extension is the reaction of acetyl chloride with vinyl chloride in the presence of AlCl₃ to form 1,1-dichloro-3-butanone, from which 1-chloro-1-butene-3-one is prepared using either NaHCO₃ or CaCO₃ (14).

\[
\text{CH}_2\text{COC}l + \text{CH}_2\text{═CHCl} \rightarrow \text{CH}_3\text{CO} - \text{CH}_2\text{-CHCl}_2 \rightarrow \text{CH}_3\text{CO} - \text{CH═CHCl}
\]

The unpleasant properties of the β-chlorovinyl ketones have hindered the technical application of these syntheses (10).

β-Chlorocrotonaldehyde is obtained in 38.5% yield by the reaction of acetone with dimethylformamide and phosphorus oxychloride or phosgene (15).

**Acetoacetaldehyde Dimethyl Acetal (I)**

The dimethyl acetal is formed from the sodium salt (II) by the action of anhydrous hydrogen chloride in methanol (64% yield) (16,17) or in methyl formate (81% yield) (7). The reaction of the sodium salt (II) with ethyl bromide in absolute ethanol gives acetoacetaldehyde diethyl acetal (18). The dimethyl acetal (I) is obtained in 70–80% yield by the treatment of β-chlorovinyl methyl ketone with potassium hydroxide in methanol at −15°C (10,11,13,19,20). The most recent technical process (21) for dimethyl acetal (I) starts with methoxybutenylene (VIII) which is readily obtained from diacetylene according to Auerhahn and Stadler (22). VIII is a stable substance in the cold.

\[
\text{HC≡C—C≡CH} + \text{ROH} \rightarrow \text{HC≡C—CH=CHOR.}
\]

VIII
Following the procedure of Franke and Seemann (28), the butynal acetal (cf. VI) is obtained from VIII by the addition of one more molecule of methanol in the presence of alkali. This acetylene derivative is hydrated in boiling aqueous methanol in the presence of an acid catalyst (mercuric sulfate) to the dimethyl acetal (I) in 80% yield. Further experiments have shown that the butynal acetal step can be bypassed. It is possible to add methanol and water to methoxybutenylene (VIII) in the presence of acid catalysts (sulfuric acid, mercuric sulfate, etc.), giving yields of I up to 85%.

\[
\begin{align*}
\text{HC} &= \text{C} - \text{CH} - \text{CHOR} \xrightarrow{\text{CH}_3\text{OH}} \text{CH}_3 - \text{C} - \text{C} - (\text{CH(OR)}_2
\end{align*}
\]

For syntheses of use in the vitamin A series the removal of water and methoxybutenone is required. This is possible by distilling three times or, better, by distillation after the addition of diethanolamine (24).

\textit{ACETOACETALDEHYDE BIS-DIMETHYL ACETAL AND }\beta\text{-METHOXYCROTONALDEHYDE DIMETHYL ACETAL (V)}

We have also obtained, besides dimethyl acetal, the 1,3-bis-dimethyl acetal from methoxybutenylene or butynal acetal, using the published procedures, but employing anhydrous methanol (21).

\[
\begin{align*}
\text{HC} &= \text{C} - \text{CH} - \text{CHOR} \xrightarrow{\text{CH}_3\text{OH}} \text{CH}_3 - \text{C} - \text{C} - (\text{CH(OR)}_2
\end{align*}
\]

Copenhaver (25) prepared the bisacetal by the reaction of orthoacetic ester with methyl vinyl ether in the presence of acid catalysts:

\[
\text{CH}_3 - \text{C(OR)}_2 + \text{CH}_3 - \text{CHOR} \xrightarrow{\text{BF}_3} \text{CH}_3 - \text{C(OR)}_2 - \text{CH}_3 - \text{CH(OR)}_2
\]

The ketal group of the bisacetal is very easily hydrolyzed by an equivalent amount of water to form I. In this manner the mixture of methoxycrotonaldehyde (V) and the bisacetal, formed by the addition of methanol to methoxybutenylene, was converted by Lautenschlager to the dimethyl acetal by careful hydrolysis with water or dilute acid at room temperature (26).

The bisacetal can be obtained by the reaction orthoformic esters with the dimethyl acetal (27).

By passing acetoacetaldehyde bisdimethyl acetal at 250° over a catalyst consisting of 20% barium oxide on 80% silica, methanol is split off to give \(\beta\)-methoxycrotonaldehyde dimethyl acetal in 81% yield (21).
Viguier (28) has described the synthesis of \( \beta \)-ethoxycrotonaldehyde diethyl acetal by the addition of ethanol to butynal diethyl acetal in the presence of sodium alkoxide in a sealed tube at 140°:

\[
\text{CH}_3\text{-C}^{\equiv}\text{C}\text{-CH(OR)}_2 + \text{ROH} \xrightarrow{\text{NaOR}} \text{CH}_3\text{-C(OR)=CH-CH(OR)}_2.
\]

**Methoxybutenone (IV)**

Methoxybutenone is a frequent by-product with 3-ketobutyraldehyde dimethyl acetal, from which it is derived by splitting off one molecule of methanol upon heating (29), especially in the presence of alkaline substances (30); quantitative conversion occurs in the presence of iron in 5 hr at 150° (31, 31a).

\[
\text{CH}_3\text{-C}^{\equiv}\text{C}\text{-CH(OR)}_2 + \text{ROH} \xrightarrow{\text{NaOR}} \text{CH}_3\text{-C(OR)=CH-CH(OR)}_2.
\]

In a 2 liter flask equipped with a column, one liter of 3-ketobutyraldehyde dimethyl acetal, 10 gm of sodium bicarbonate, and 10 gm of iron turnings (Baustahl St 0037) are slowly heated in an oil bath at 500 mm. Under these conditions methanol distills. After about 5 hr the temperature in the flask reaches the boiling point of methoxybutenone, which is about 160° at this pressure. The temperature of 160° is maintained for 1 hr. The distilled amount of methanol is often somewhat more than calculated. After cooling the mixture is filtered and finally distilled. The yield is 90% (31a).

The compound also is obtained from methoxybutenylene by careful hydration of the triple bond below 50° (32):

\[
\text{HC}^{\equiv}\text{C}\text{-CH-CHOR} \xrightarrow{\text{H}_2\text{O}} \text{CH}_3\text{-CO-CH=CHOCH}_3.
\]

Yamada has obtained methoxybutenone (IV) from the sodium salt (II) and dimethyl sulfate (33).

The reactions based on methoxybutenylene and diacetylene are summarized in the diagram; the 1,3-dimethoxybutadiene is not obtainable by these reactions. The "boxed" compounds are available commercially on a large scale.

On the basis of experimental results it is possible to compare the reactivity of acetals of acetoacetaldehyde. The bisacetal and the methoxyCrotonaldehyde acetal (V), in which the oxo group is not free, are less reactive than the dimethyl acetal (I) and the methoxybutenone (IV). Especially in an alkaline medium or in reaction with basic reactants, the bisacetal and V react slowly, while I and IV react readily.
In acid medium the bisacetal and the methoxycrotonaldehyde acetal (V) react like I and IV, because of the rapid hydrolysis of the ketals and enol ethers. I and IV differ only slightly in their reactivity; only the formation of Schiff bases occurs faster with IV than with I.

From the summary it can be seen, that the starting materials methoxybutenyne (VIII) and butynal acetal (VI), used in the preparation of the acetal of acetoacetaldehyde, can be transformed in acid medium to the intermediate, acetoacetaldehyde. In the absence of a suitable reactant, triacetylbenzene is formed. If reactive substances are present in the reaction mixture, then the formation of heterocyclic compounds is possible.

1-AMINO-1-BUTEN-3-ONE

This class of substances can be obtained by the reaction of ammonia or amines, with an alkoxybutenone (34) (Procedure 1), or with the acetal I (34a) (Procedure 2).

Procedure 1. Ammonia is passed through 1000 gm of freshly distilled methoxybutenone for 5 hr. The temperature is kept at 0-20° by ice cooling. Vacuum distillation yields 85-90% of the aminobutenone, b.p. 95-101°/15 mm.

Procedure 2. The acetal, I, 132 gm, is mixed with 5 ml of a saturated aqueous solution of potassium carbonate and cooled to -35°. At this temperature ammonia is passed in with stirring (within about 3 hr) until the volume is doubled. The temperature is allowed to rise within 2 hr to -10° while stirring and passing in more ammonia. After addition of 125 ml of saturated potassium carbonate solution, the mixture reaches room temperature and should be well mixed. The upper layer is dissolved in ether and dried over potassium carbonate. Distillation yields 67 gm
SYNTHESES WITH ACETOACETALDEHYDE

(79%) of 1-amino-1-buten-3-one, a colorless highly refractive liquid, b.p. 44°/0.5 mm; \( n_D^{20} = 1.5585; d_4^{20} = 1.022. \)

If an aminobutenone is dissolved in benzene, the values of the dielectric constant are lowered (35). This means that the equilibrium which prevailed in the pure liquid is now shifted by the presence of benzene to give a less polar mixture:

\[
\begin{align*}
\text{CH}_2\text{=C-CH=CH-} & \text{N-H} \rightarrow \text{CH}_2\text{=C-CH=CH-} & \text{N-H} \\
\mid O & \text{H} & \mid O & \text{H}
\end{align*}
\]

The investigators A. N. Nesmeyanov and N. K. Kochetkov found that the reaction of 1-chlorobutenone with ammonia and amines leads to aminobutenones in yields up to 90% (36-38). From the fact that the refractive index increases after distillation, the conclusion was drawn that a tautomeric equilibrium sets in favoring \( \text{RC(OH)=CHCH=NH} \) (39). The IR spectra of some aminobutenones also support this tautomerism (40).

The reaction of chlorovinyl methyl ketone with tertiary amines leads to ammonium salts (41).

\[
\text{CH}_3\text{COCH=CH-N(CH}_3\text{)}_3\text{Cl} \]

The reaction of \( \text{N,N-dimethylamino-1-buten-3-one} \) with methyl iodide gives the corresponding iodide (42). The higher ketobutenyltrialkyl ammonium salts can be converted to the corresponding hydroxymethylene ketones at high temperatures in the presence of water (42). From \( \text{CH}_3\text{COCH=CHN(CH}_3\text{)}_3\text{Cl} \) and potassium cyanide, \( \text{CH}_3\text{COCH=CHCN} \) is obtained (43).

The aminobutenones react readily; on heating with water triacetylbenzene is formed (37); on hydrogenation the amino group is split off (44). Our own experimental results confirm the statements of the Russian investigators. The aminobutenones did not react as dienophiles with cyclopentadiene (44); they are suitable for ring closure reactions to form heterocyclic compounds which will be described.

Noteworthy is the reaction of 1-chlorobutenone with aniline: in the molar ratio of 1:1, anilinobutenone (45), \( \text{CH}_3\text{COCH=CHNHCH}_3\text{H}_5 \), is obtained; in the molar ratio of 1:2, the dianil, \( \text{CH}_3\text{C(=NC}_6\text{H}_5\text{)CH=CHNHCH}_3\text{H}_5 \) (46). The dianils cyclize with sulfuric acid to quinoline derivatives:

\[
\begin{align*}
\text{C}_6\text{H}_4\text{NH} & \text{CH} \\
\text{C} & \text{CH} \rightarrow \text{C}_6\text{H}_4\text{NH}_2
\end{align*}
\]
If ketobutyraldehyde glycolacetal is treated with a primary amine, the keto group reacts with the formation of (47):

\[
\begin{align*}
\text{CH}_2\text{C} & \text{H}-\text{C} \equiv \text{CH} \quad \text{O-CH} \quad \text{NR} \\
\text{O-CH} & \quad \text{CH} \\
\end{align*}
\]

Interestingly, in the reaction of aminobutenone with an organometallic compound, the amino group is exchanged for the organic group of the organometallic. Example 1 is from work of Jutz (48) and 2. from Kochetkov (11).

\[
\begin{align*}
\text{CH}_3\text{CO-CH=CH-N(CH}_3\text{)} & \text{-C}_2\text{H}_5 + \text{C}_2\text{H}_5\text{Li} \rightarrow \\
\text{CH}_3\text{CO-CH=CH-C}_2\text{H}_5 & \\
\text{CH}_3\text{CO-CH=CH-NR}_3 + \text{CH}_3\text{MgI} \rightarrow \text{CH}_3\text{CO-CH=CH-CH}_3 \\
\end{align*}
\]

The aminobutenones act as stabilizers for acrylic acid and its esters (49).

**Syntheses in the Aliphatic Series**

Plieninger and Müller reacted the acetal (I) with lead tetraacetate in an attempt to prepare the methyl homolog of reductone (50). A 40% yield of A was obtained and only a little of B, although A could be converted to B with methanol.

\[
\begin{align*}
\text{CH}_3\text{CO-CH=CH(OCH}_3\text{)OCOCH}_3 + \text{CH}_3\text{OH} \rightarrow \text{CH}_3\text{CO-CH=CH(OCH}_3\text{)}_2 \quad \text{CH}_3\text{CO-CH=CH(OCH}_3\text{)}_2
\end{align*}
\]

B gives \(\text{CH}_3\text{CHOHCHOHCH(OCH}_3\text{)}_2\) with \(\text{LiAlH}_4\).

Kochetkov and Nifant’ev (51) obtained A in a similar manner. The action of bromine on acetoacetaldelyde in the presence of \(\text{CaCO}_3\) yielded \(\alpha\)-bromoacetoacetaldelyde. When the glycol acetal was used the acetal group remained intact and \(\alpha\)-bromoacetoacetaldelyde glycol acetal was formed.

\[
\begin{align*}
\text{CH}_3\text{CO-CHBr-CHO} & \rightarrow \text{CH}_3\text{CO-CHBr-CH} \quad \text{O-CH}_3 \\
\text{O-CH} & \quad \text{CH}
\end{align*}
\]

Grignard reagents attack the oxo group in the normal manner.

\[
\begin{align*}
\text{C}_2\text{H}_4\text{O-C≡C-MgBr} + \text{C}_2\text{H}_4\text{COCCH}_3\text{H(OCH}_3\text{)}_2 \rightarrow \\
\text{C}_2\text{H}_4\text{O-C≡C-CH}_3-\text{C(OH)}-\text{CH}_3-\text{CH(OCH}_3\text{)}_2
\end{align*}
\]

As expected, this compound forms the ester, \(\text{C}_2\text{H}_4\text{OCOCCH}_2\text{C(\text{CH}_3)} = \text{CHCHO}\), with acids at higher temperature (52).

1-Isobutoxy-2-buten-3-one, formed from sodium formylacetone and
isobutyl alcohol in the presence of a small amount of p-toluenesulfonic acid, gives β-methylcrotonaldehyde in 59% yield when treated with methylmagnesium bromide in absolute ether, followed by hydrolysis (53).

A group of investigators at Eastman Kodak carried out work in the carotinoid field using acetoacetaldehyde acetal. The reaction of acetal (I) with propargyl bromide (54) in the presence of mercury-activated magnesium occurs in the normal way, at the carbonyl group, leading to a component of the geraniol and phytol series:

\[
\text{CH}_3 \text{CH} = \text{C}-\text{CH}=\text{C}(\text{OH})-\text{CH}_3-\text{CH(OCH}_3)_2 .
\]

In the vitamin A series the acetal, in four preparative procedures, has been joined in each instance to a different molecule to furnish the necessary intermediates. These procedures are as follows [1. (55); 2. (56); 3. (57); 4. (58)]:

1. 
\[
\text{RCH}=\text{CHC}+\text{HC}=\text{CCH}_2\text{CH(OCH}_3)_2
\]
(A prepared from the acetal and propargyl bromide)

2. 
\[
\text{RCH}=\text{CHC}=\text{CH}_2+\text{CH}=\text{CCH}=\text{C(OCCH}_3)_2
\]

3. 
\[
\text{RCH}=\text{CHC}=\text{CHO}+\text{CH}=\text{CCH}=\text{C(OCCH}_3)_2
\]

4. 
\[
\text{RCH}=\text{CHC}=\text{CHO}+\text{HC}=\text{CCH}_2\text{CH(OCH}_3)_2
\]
(B prepared from the acetal and acetylene)

In procedure 3 a side-chain methyl group has to be introduced by reaction with methylmagnesium iodide.

The triple bond is hydrogenated to the double bond with Pd/charcoal

\[
\text{HOCH}_3 \rightarrow \text{CH}_2\text{CH}=\text{C}=\text{CH} \rightarrow \text{CH}_2=\text{CHCH}=\text{C}=\text{CHCHOCH}_3
\]

Vitamin-A-Aldehyde
<table>
<thead>
<tr>
<th>Reactant</th>
<th>Reaction product</th>
<th>Bis-acetal</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
<th>V$^a$</th>
<th>VI</th>
<th>VII</th>
<th>VIII</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Aromatics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetoacetaldehyde</td>
<td>1,3,5-Triacetylbenzene</td>
<td>+</td>
<td>90%</td>
<td>46%</td>
<td>−</td>
<td>85%</td>
<td>+</td>
<td>50%</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Acetoacetic ester</td>
<td>m-Cresotic Acid</td>
<td>−</td>
<td>15%</td>
<td>65%</td>
<td>39%</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>2. Pyrylium salts</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>β-Naphthol</td>
<td>2-Methyl-5,6-naphtho(1,2)pyrylium</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>74%</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>55%</td>
</tr>
<tr>
<td></td>
<td>chloride</td>
<td></td>
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<td></td>
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<td></td>
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<tr>
<td>3. Pyridine ring closure</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Cyanacetamide</td>
<td>3-Cyano-6-methyl-2-pyridone</td>
<td>79%</td>
<td>95%</td>
<td>68%</td>
<td>−</td>
<td>80%</td>
<td>35%</td>
<td>−</td>
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<td>−</td>
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<tr>
<td>Aminoerotic ester</td>
<td>Lutidinecarboxylic ester</td>
<td>35%</td>
<td>50%</td>
<td>25%</td>
<td>−</td>
<td>40%</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Acetylacetone imine</td>
<td>3-Acetyl-2,6-dimethylpyridine</td>
<td>−</td>
<td>47%</td>
<td>−</td>
<td>−</td>
<td>40%</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Diacetonitrile</td>
<td>3-Cyano-2,6-dimethylpyridine</td>
<td>−</td>
<td>41%</td>
<td>−</td>
<td>−</td>
<td>25%</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Aminobutenone</td>
<td>5-Acetyl-2-methylpyridine</td>
<td>−</td>
<td>42%</td>
<td>40%</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Malonic ester iminoether</td>
<td>2-Amino-6-methylnicotinic ester</td>
<td>−</td>
<td>25%</td>
<td>−</td>
<td>−</td>
<td>20%</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>β-Naphthylamine</td>
<td>6,7-Benzolepidine</td>
<td>−</td>
<td>−</td>
<td>30%</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
</tbody>
</table>
4. Ring closure to 4-methylpyrimidine (=Z)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Product</th>
<th>Yield (40%)</th>
<th>Yield (70%)</th>
<th>Yield (85%)</th>
<th>Yield (95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formamide</td>
<td>4-Methylpyrimidine</td>
<td>—</td>
<td>70%</td>
<td>40%</td>
<td>40%</td>
</tr>
<tr>
<td>Urea</td>
<td>2-Hydroxy-Z</td>
<td>86%</td>
<td>85%</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Thiourea</td>
<td>2-Mercapto-Z</td>
<td>95%</td>
<td>95%</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Guanidine</td>
<td>2-Amino-Z</td>
<td>—</td>
<td>96%</td>
<td>51%</td>
<td>80%</td>
</tr>
<tr>
<td>Benzaldehydrazinoformamidine</td>
<td>2-Hydrazino-Z</td>
<td>—</td>
<td>—</td>
<td>25%</td>
<td>—</td>
</tr>
<tr>
<td>Dicyandiamide</td>
<td>2-Cyanamino-Z</td>
<td>—</td>
<td>—</td>
<td>75%</td>
<td>—</td>
</tr>
<tr>
<td>Sulfaguanidine</td>
<td>Sulfamerazine, Methyldebenal</td>
<td>—</td>
<td>82%</td>
<td>78%</td>
<td>82%</td>
</tr>
<tr>
<td>Benzamidine</td>
<td>2-Phenyl-Z</td>
<td>—</td>
<td>53%</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>2-Aminopyrimidine</td>
<td>1-Azadehydroquinolinium perchlorate</td>
<td>—</td>
<td>72%</td>
<td>75%</td>
<td>—</td>
</tr>
</tbody>
</table>

5. Syntheses of 5-membered rings

<table>
<thead>
<tr>
<th>Compound</th>
<th>Product</th>
<th>Yield (30%)</th>
<th>Yield (44%)</th>
<th>Yield (53%)</th>
<th>Yield (61%)</th>
<th>Yield (64%)</th>
<th>Yield (68%)</th>
<th>Yield (75%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrazine</td>
<td>3-(5-)Methylpyrazole</td>
<td>68%</td>
<td>92%</td>
<td>+</td>
<td>—</td>
<td>+</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Phenylhydrazine</td>
<td>3-Methyl-1-phenoxyrazole</td>
<td>—</td>
<td>85%</td>
<td>35%</td>
<td>—</td>
<td>+</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>p-Nitrophenylhydrazine</td>
<td>3-Methyl-1-(p-nitrophenyl)pyrazole</td>
<td>—</td>
<td>64%</td>
<td>—</td>
<td>+</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Methylhydrazine</td>
<td>1,3-Dimethylpyrazole</td>
<td>—</td>
<td>61%</td>
<td>+</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Semicarbazide</td>
<td>3-Methyl-1-pyrazolecarbonamide</td>
<td>80%</td>
<td>95%</td>
<td>+</td>
<td>—</td>
<td>—</td>
<td>30%</td>
<td>—</td>
</tr>
<tr>
<td>Hydroxylamine</td>
<td>3- and 5-Methylisoxazole</td>
<td>64%</td>
<td>68%</td>
<td>+</td>
<td>+</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Phenyl azide</td>
<td>4-Acetyl-1-phenyltriazole</td>
<td>—</td>
<td>44%</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

*a These reactions were carried out with ethoxycrotonaldehyde acetal.

*b These reactions were carried out with 1-ethoxy-1-buten-3-one.
(quinoline), according to Lindlar. Hydroxyl groups are removed with POCls with formation of water, yielding more double bonds; hydrolysis of the acetal group and finally isomerization with alkaline substances leads to vitamin A aldehyde, which is reduced to the alcohol with LiAlH$_4$.

Eiter and Truscheit recently used the acetal (I) to form a vitamin A derivative in 90% yield (58a). Patterned after the Wittig phosphine-methylene method, Pommer and Sarnecki (59) attained similar objectives with the use of 1-methoxy-3-butenone, 1-chlorobutenone, and other oxo compounds.

**Ring-closure Syntheses**

The ring-closure reactions are the most important transformations of the intermediates and derivatives of acetoacetaldehyde. Table 2 shows the yields obtained by the reaction of acetoacetaldehyde bisacetal and of the substances I–VIII with the compounds named in the first column (+ denotes that the reaction was carried out, but no yield was given).

The reaction procedures are described below; H. Henecka (59a) has dealt with the reaction mechanisms.

**Synthesis of Aromatics**

1,3,5-Triacetylbenzene

The formation of this compound from the sodium enol salt II by the action of glacial acetic acid was first described by Claisen (5). Fischer and Fink obtained the compound by the treatment of the diethyl acetal with glacial acetic acid (60). Yields of 75–90% are obtained from I or IV by heating with water, as described in a German patent (61) and by Royals and Brannock (8). The preparation of the three semicarbazones is described by F. Mietzsch and H. Schmidt in German patent 922,102 (Farben-Fabriken, Bayer) [Chem. Abstr. 51, 12971 (1957)].

1,3,5-Tris(α-hydroxyethyl) benzene is obtained from triacetylbenzene by hydrogenation. Subsequent splitting out of water forms 1,3,5-trivinylbenzene which, on addition of styrene, polymerizes to give insoluble resins which swell only a little (62). The entire process for the manufacture of 1,3,5-trivinylbenzene from acetone and methyl formate to form triacetylbenzene, the reduction of the latter to triethylolbenzene and the splitting out of water has been patented (63).
SYNTHESES WITH ACETOACETALDEHYDE

13

m-CRESOTIC ACID

Prelog, Metzler, and Jeger (64) obtained the compound in 55–65% yield from the sodium salt, II, and acetoacetic ester followed by hydrolysis. We obtained only a 15% yield of the ester from I and acetoacetic ester in the presence of sodium alkoxide. Kochetkov, Kudryaskov, and Nesmeyanov (65) obtained the compound in 39% yield from acetoacetic ester and 1-chlorobutenone.

2-METHYLNAPHTHALENE

The reaction of acetal I with benzylmagnesium chloride furnishes a route to the naphthalene series (66).

[Chemical structure of the reaction]

The yields are better (67) with glycol acetals,

[Chemical structure of the reaction]

Synthesis of Rings Containing Oxygen

An important contribution to the knowledge of β-keto acetals was furnished by Burness (68) with his synthesis of 3-methylfuran:

\[(CH_2O)_2CH-CH_3+COCH_3+CH_2ClCOOCH_3 \rightarrow (NaOCH_2) \rightarrow 80\% \]

[Chemical structure of the reaction]

The Darzens reaction proceeds as well with the methoxybutenone, IV; however, neither acetoxybutenone nor sodium formylacetone react with chloroacetic ester.

The ring closure to 3-methylnaphtho[2,1-b]pyrilium chloroferrate (III) from 2-naphthol occurs with 1-butyn-3-one (69) and also with chlorovinyl methyl ketone (70, 71).
3-Cyano-2-hydroxy-6-methylpyridine \((R = \text{CN}, R' = \text{OH})\). This was first obtained by Dornow (72) from cyanacetamide and ethoxyeretonaldehyde acetal in 35\% yield. Perez-Medina, Mariella, and McElvain (73), starting with II and cyanacetamide in the presence of a catalytic amount of piperidine acetate, obtained a 68\% yield. From acetoacetaldehyde bisacetal (74) (from VI or VIII) and cyanacetamide in the presence of piperidine acetate, we reached yields of 79–95\%. The reaction of cyanacetamide with N,N-dialkylaminobutenones also leads to 3-cyano-2-hydroxy-6-methylpyridine (75).

Ethyl 2,6-dimethylnicotinate \((R = \text{COOC}_2\text{H}_5, R' = \text{CH}_3)\). Rabe (76) obtained the ester in 25\% yield by heating II, acetoacetic ester, and ammonia in alcohol. Dornow (77) obtained the ester from ethoxyeretonaldehyde acetal and ethyl aminocrotonate in 40\% yield. The preparation of ethyl 2,6-dimethyl nicotinate from I, acetoacetic ester, and ammonia in over 50\% yield has been patented (78). From acetoacetaldehyde bisacetal and an ester of aminocrotonic acid, an ester of lutidinecarboxylic acid is obtained. The preparation from I and ethyl aminocrotonate proceeds as follows.

I, 132 gm, 130 gm of ethyl aminocrotonate and 15 gm of ammonium acetate are heated to 40–50\° in a water bath and with stirring 30 gm of glacial acetic acid is added. Then water is added and the alcohol removed by steam distillation. The residue is decomposed with dilute sulfuric acid, heated for 20 min on the water bath and, after cooling, extracted with ether. The acid solution is made alkaline with sodium hydroxide and extracted several times with ether. The ether extracts are dried, then concentrated. On distillation the ethyl 2,6-dimethylnicotinate boils at 123–125°/15mm. Yield: 50\%. The m.p. of the picrate is 138°.

3-Acetyl-2,6-dimethylpyridine \((R = \text{COCH}_3, R' = \text{CH}_3)\). Dornow (77) obtained this compound from acetylacetonimine and ethoxyeretonaldehyde acetal in 30–40\% yields. With I, acetylacetonimine reacts in an analogous manner. A mixture of 9.9 gm of acetylacetonimine, 13.2 gm
of I, 1.5 gm of ammonium acetate, and 1 gm of glacial acetic acid is heated for 12 hr in the water bath. The cooled solution is acidified with dilute mineral acid and extracted with ether to remove impurities; finally the solution is made alkaline and extracted several times with ether. The ether extracts are dried; on evaporation an oil is obtained which distills at 110-112°/13 mm. A yield of 7 gm (47%) of 3-acetyl-2,6-dimethylpyridine is obtained. Crystals which are volatile are formed from wet ether, m.p. 42° (dihydrate); picrate, m.p. 129°.

3-Cyano-2,6-dimethylpyridine (R = CN, R' = CH₃). This pyridine derivative is obtained according to Dornow (77), from diacetonitrile and ethoxycrotonaldehyde acetal in 25% yields. The compound I reacts in a similar manner.

Diacetonitrile (8.2 gm), 13.2 gm of I, 1 gm of ammonium acetate, and 1 gm of glacial acetic acid are warmed for 8 hr in a water bath. After cooling the reaction mixture is acidified with dilute mineral acid and extracted with ether to remove impurities. The solution is then made alkaline and again extracted with ether. The ether extracts are dried; then the ether is distilled. There remains an oil, which quickly crystallizes (m.p. 83°) and consists of 3-cyano-2,6-dimethylpyridine. Yield: 5.5 gm (41%); picrate, m.p. 180°.

5-Acetyl-2-methylpyridine (R = COCH₃, R' = H). Benary and Psille (79) obtained a 40% yield from the sodium salt II which was treated in ether with a solution of ammonium acetate in glacial acetic acid. Aminobutenone also reacts with I in the presence of glacial acetic acid to form 5-acetyl-2-methylpyridine (from the investigations of D. Tietjen).

A mixture of 38 gm of glacial acetic acid, 11 gm of ammonium acetate, 47 gm of I, and 30 gm of aminobutenone is stirred for 5 hr at 80°. The mixture is cooled, made weakly alkaline with sodium hydroxide, and extracted with ether. After the evaporation of the ether, 5-acetyl-2-methylpyridine remains as an oil, which distills at 103-105°/12 mm. B.p. 231-233°/760 mm. Yield: 20 gm (42%).

Ethyl 2-amino-6-methylnicotinate (R = COOC₂H₅, R' = NH₂) is obtained, according to Dornow and Karlson (80), from ethoxycrotonaldehyde acetal and ethyl β-amino-β-ethoxyacrylate. It is obtained from I in an analogous way. 2-Amino-6-methylnicotinamide was obtained by Dornow and Neuse from sodium formylacetone (II) and 2-aminoacetamide in 56% yield (81).

6-Butyryl-2-methylpyridine (R = H, R' = COC₃H₇). Hardegger and Nikles (82) obtained a mixture of 6-butyryl-2-methylpyridine (small amount) and 6-butyryl-2-propylpyridine by reaction of III with 1-amino-1-hexen-3-one.

3,5-Diacetyl-1,4-dihydro-1,4-diphenylpyridine was obtained by Inoue
(83) in 37% yield by the condensation of 2 moles of 1-anilinobuten-3-one with 1 mole of benzaldehyde in the presence of piperidine.

6,7-Benzolepidine. From β-naphthylamine and sodium formylacetone (II) a 70% yield of 1-(2-naphthylimino)-3-butanone is obtained, which cyclizes with HF to 6,7-benzolepidine (6).

**Synthesis of Pyrimidine Derivatives**

![Chemical Structure]

4-Methylpyrimidine (R = H). H. Bredereck and co-workers (84) obtained 4-methylpyrimidine in 70% yield from the acetal (I) and formamide at 180° with the addition of NH₄Cl; with 1-ethoxy-1-buten-3-one, 1-dimethylaminobuten-3-one or 1-chlorobuten-3-one a 40% yield is obtained.

A solution of 20 gm of acetoacetaldehyde dimethyl acetal (I) in 50 gm of formamide is added dropwise over a 5 hr period to a solution of 80 gm of formamide, 10 gm of ammonium chloride, and 3 ml of water at 180°. After being heated for an additional 2 hr and then diluted with sodium hydroxide, the mixture is extracted with chloroform for 15 hr. Distillation gives 10 gm (70%) of 4-methylpyrimidine, b.p. 140-142° (84).

Yields of 58-66% of 4-methylpyrimidine are obtained by the passage of acetoacetaldehyde acetal and formamide over Al₂O₃ or montmorillonite at 200-240° (85).

2-Hydroxy-4-methylpyrimidine hydrochloride (R = OH). Urea and I in an alcohol solution react in the presence of concentrated hydrochloric acid to form 2-hydroxy-4-methylpyrimidine hydrochloride. The bisacetal reacts in the same manner (74). The reactions of the bisacetal with amidines have been described by Copenhaver (86, 87).

2-Mercapto-4-methylpyrimidine hydrochloride (R = SH). This compound is formed in an analogous manner from I or the bisacetal and thiourea (74); similarly, methoxybutenylene (VIII) reacts almost quantitatively with thiourea. The methylation of the thiol group with dimethyl sulfate and the removal of the CH₃S-group by reduction leads to 4-methylpyrimidine (88). 2-Mercapto-4-methylpyrimidines having a substituent on the sulfur are found to be good vulcanization accelerators (89). When morpholine is present as a substituent, the material has an antiscorching effect (90).

2-Amino-4-methylpyrimidine (R = NH₂). This pharmaceutically important starting material was obtained by Benary in 51% yield by shak-
ing the sodium salt II and guanidine nitrate in alcohol (91). Mauss and Andersag (92) used the methoxybutenone (VIII) and guanidine sulfate, which react in sulfuric acid medium to give a 50% yield. The highest yield (96%) was obtained by the treatment of the acetal (I) with guanidine, utilizing the azeotropic removal of water with xylene (93).

2-Hydrazino-4-methylpyrimidine \((R = \text{NHNH}_2)\). Sodium formylacetone reacts with benzylideneaminoguanidine to give 2-benzylidinehydrazino-4-methylpyrimidine, from which the 2-hydrazino-4-methylpyrimidine is obtained in 25% yield (94).

2-Cyanamino-4-methylpyrimidine \((R = \text{NHCN})\). This compound is prepared from dicyandiamide and the acetal (I) in the presence of sodium ethoxide. Twenty-one grams of dicyandiamide are treated with a solution of 33 gm of I in 150 ml of ethanol. To this mixture is added a solution of 5.7 gm of sodium in 100 ml of ethanol. The mixture is refluxed for several hours and the cooled solution is then neutralized with 15 gm of glacial acetic acid. The crystalline mass is filtered off after 30 min. The product is recrystallized from water. Yield: 25.5 gm (75%). It decomposes without definite melting around 200°.

When this compound is heated with dilute mineral acids, the cyano group is attacked to form 4-methyl-2-ureidopyrimidine \((R = \text{NHCONH}_2)\). If concentrated hydrochloric acid is used and the mixture heated a short time, 2-amino-4-methylpyrimidine is then the main product.

p-Aminobenzenesulfonamide-4-methylpyrimidine \((R = \text{NHSO}_2\text{C}_6\text{H}_4\text{-NH}_2-p)\). This sulfonamide, known as Methyldebenal, Pyrimal M, and Sulfamerazine, was obtained by the Japanese workers (17), as well as by Mauss and Leuchs (95), from sulfaguanidine

\[
\text{H}_2\text{N}-\overset{\text{SO}_2-\text{NH-}}{\text{C(=NH)}}_{\text{(-NH)}}-\text{NH}_2
\]

and the acetal (I) in 70–80% yield. The resulting monoanil from aniline and the sodium salt (II) was treated with guanidine nitrate by Ishikawa and Kano (96) to form 2-amino-4-methylpyrimidine which was converted to Methyldebenal with sulfaguanidine. The same substance is obtained by the reaction of methoxybutenone (IV) (33) or chlorovinyl methyl ketone (III) (97) with \(p\)-aminobenzene-sulfaguanidine.

4-Methyl-2-phenylpyrimidine \((R = \text{C}_6\text{H}_5)\). This compound had not yet been synthesized directly (98). It is prepared from benzamidine and the acetal (I) as follows.

Benzamidine hydrochloride (15.6 gm) is dissolved in 75 ml of ethanol and treated with a solution of 2.5 gm sodium in 75 ml of ethanol. The sodium chloride is filtered off, the filtrate treated with 13.2 gm of (I)
and the mixture refluxed for 3 hr. After cooling the solution is neutralized with glacial acetic acid, the ethanol removed by steam distillation, and the residue made alkaline with potassium hydroxide. After extraction with ether and drying over potassium carbonate, distillation follows. At 139–141°/13 mm there is obtained 9 gm (53%) of 4-methyl-2-phenylpyrimidine. On cooling crystals are obtained, m.p. 22°. Physical data for 4-methyl-2-phenylpyrimidine obtained in another way are: b.p. 279°/762 mm; m.p. 22.5° (98).

1-Azadehydroquinolininium perchlorate is formed from I or III with 2-aminopyridine in the presence of perchloric acid in 72 or 75% yield (99).

![Synthesis of Nitrogen-Containing Five-Membered Rings](image)

3-(or 5-)Methylpyrazol (R = H). Rothenburg (100) obtained the compound from the sodium salt (II) and hydrazine acetate. From the bisacetal and hydrazine sulfate a yield of 68% is obtained. It is prepared from I and hydrazine sulfate as follows.

To a suspension of 130 gm of hydrazine sulfate in 160 ml of water 132 gm of the acetal (I) is added slowly and dropwise. The mixture is then heated at 60° for 2 hr, cooled, made alkaline, and extracted with ether. By distilling at 104–106°/18 mm there is obtained 75 gm (92%) of 3-(5-)methylpyrazol.

Methoxybutenyne (VIII) also forms the methylpyrazole with hydrazine sulfate.

A mixture of 130 gm of hydrazine sulfate, 80 ml of water, 250 ml of ethanol, and 2 ml of concentrated sulfuric acid is stirred and heated to 80–85°. Methoxybutenyne (82 gm) is added slowly to the mixture. When the addition is complete, stirring is continued 30 min longer, the alcohol is removed by steam distillation, the residue made alkaline and extracted several times with ether. Evaporation of the ether leaves an oil, which distills at 100–102°/15 mm. Yield: 54 gm (66%).

3-Methyl-1-phenylpyrazole (R = C₆H₅). This compound is formed,
SYNTHESES WITH ACETOACETALDEHYDE

according to Claisen and Roosen (101), from phenylhydrazine salts and II; von Rothenburg (100) obtained the compound from ethoxycrotonaldehyde acetal and phenylhydrazine. Auwers and Hollmann (102) obtained an 86% yield by using the enol benzoate. The latter is obtained from the sodium salt (II) and benzoyl chloride. The methylphenylpyrazole is obtained from I as follows.

A solution of 45 gm of concentrated sulfuric acid in 110 ml of water is added dropwise to 108 gm of phenylhydrazine. Neglecting the precipitated sulfate 132 gm of I is added dropwise. The temperature rises; the salt disappears. The mixture is heated at 70° for 2 hr, then made alkaline with sodium hydroxide and extracted with ether. On distillation there is obtained at 138–141°/18 mm a yield of 36 gm (85%) of the methylphenylpyrazole. The largest part (ca. 90%) of this crystallizes on cooling, m.p. 36°.

p-Nitrophenylhydrazine forms with I a 64% yield of the 3-methyl-1-p-nitrophenylpyrazole (103). The same substance is formed also from III (104).

1,3-Dimethylpyrazole (R = CH₃). According to Burness (93) the reaction of methylhydrazines with the acetal (I) in acid medium always gives the 1,3-dimethylpyrazole, whereas in an alkaline medium a mixture of the 1,3- and 1,5-isomers is obtained.

Methylhydrazine (3 gm) is added dropwise to 8.6 gm of I. The temperature of the mixture rises to 40°; it is heated for 10 min on the steam bath, 5.5 gm of crude methylhydrazone is dissolved in 5 ml of water, decomposed with 5.3 gm of 6N hydrochloric acid and heated on the steam bath for 20 min. On addition of 2.4 gm of 50% sodium hydroxide an oil separates which is extracted with ether. After drying and distilling there is obtained a 61% yield of 1,3-dimethylpyrazole (93). B.p. 143–145°; nD²⁵ 1.4734. M.p. of picrate: 170–171°.

Auwers and Hollmann obtained a mixture of 1,3- and 1,5-dimethylpyrazole in the reaction of sodium formylacetone with methylhydrazine (102). 1-Cyano-3-butenone, which is converted to 1-aminobutenone with secondary amines, also reacts with hydrazine to form 3-methylpyrazolone (105).

3-Methyl-1-pyrazolecarboxamide (R = CONH₂). This substance is obtained, according to Auwers and Daniel (106), from semicarbazide hydrochloride or from the disemicarbazone acetoacetalddehyde on treatment with sulfuric acid. It is also obtained from ethoxycrotonaldehyde acetal and semicarbazide hydrochloride, according to Viguier (28). From the acetal (I) and semicarbazide hydrochloride the compound is prepared as follows.

Sixty-six grams of I in 70 ml of water is treated with a solution of
56 gm of semicarbazide hydrochloride in 90 ml of water with ice cooling. After a few minutes an exothermic reaction begins and the methylpyrazole-1-carboxamide precipitates. After several hours the crystals are filtered and washed with a little water. The yield is almost quantitative. The compound melts at 96°, then solidifies, and melts again at 127°, even when the melting point determination is repeated. The compound is probably not the 5-methyl-, but the 3-methylpyrazolecarboxamide.

The corresponding thiocarboxamide is obtained from I and thiosemicarbazide (93). By using aminoguanidine the expected pyrazole \[ R = C (\text{= NH}) \text{NH}_2 \]$ is not obtained; instead 1,3-butanedione-bis(guanylhydrazone) is isolated (93).

*Methylisoxazole.* The mixture of 3- and 5-methylisoxazole is obtained by the reaction of II with hydroxylamine hydrochloride (107). This mixture, chiefly the 5-isomer, is also obtained from the acetal (I) and hydroxylamine hydrochloride.

A solution of 69 gm of \( \text{NH}_2 \text{OH-HCl} \) in 70 ml of water is added dropwise to 132 gm of I and 60 ml water. The reaction mixture becomes warm (about 50°C). When the addition is complete, the mixture is heated at 60-70° for 2 hr. The mixture is cooled, made alkaline with sodium hydroxide and extracted with ether. After evaporation of the ether an oil remains, which is distilled at atmospheric pressure. The fraction which comes over between 117° and 122° consists of a mixture of 3- and 5-methylisoxazole (the 5-isomer predominating). The yield is 57 gm (68%).

5-Methylisoxazole is also made from 1-dialkylamine-3-butenone or chlorovinyl methyl ketone and hydroxylamine; on treatment with sodium ethoxide it is converted quantitatively to the sodium salt of the enolic acetoacetonitrile (108).

4-Acetyl-1-phenyltriazole was obtained by Kochetkov from chlorovinyl methyl ketone and phenyl azide (109).

1-Acetyl-3-methylpyrrole. Plieninger and Bühler (110) obtained this compound as follows:

\[
\begin{align*}
\text{CH}_2\text{COCH}_3\text{CH(OCH}_3)_2 & \quad + \quad \text{HCN} \quad \rightarrow \quad \text{CH}_3\text{C-C=CHCN} \\
& \quad \text{ONa}
\end{align*}
\]
During the reduction of the cyanohydrin with lithium aluminum hydride the hydroxyl group is protected with dihydropyran.

**Reaction of Intermediates**

Several significant reactions of two important intermediates should be considered. These materials are chlorovinyl methyl ketone (III) and 1-methoxy-1-buten-3-yne (VIII).

A. N. Nesmeyanov and co-workers (111) investigated fully the reactivity of chlorovinyl methyl ketone; they obtained, e.g., with CH₃OC₆H₄ in the presence of SnCl₄ (111):

\[
\text{CH₃-O-CH=CH-COCH₃} \\
\text{CH₃-O-CH=CH-COCH₃} \\
\text{CH₃-O-CH=CH-COCH₃} \\
\text{CH₃-O-CH=CH-COCH₃}
\]

with CH₃OC₆H₄CH₃-p in the presence of SnCl₄:

\[
\text{CH₃-O-CH=CH-COCH₃} \\
\text{CH₃-O-CH=CH-COCH₃} \\
\text{CH₃-O-CH=CH-COCH₃} \\
\text{CH₃-O-CH=CH-COCH₃}
\]

with β-naphthol in the presence of NaOH (71):

\[
\text{CH₃-O-CH=CH-COCH₃} + \text{CH₃-O-CH=CH-COCH₃}
\]

with xylene in the presence of AlCl₃ (112):

\[
\text{CH₃} \\
\text{CH₃} \\
\text{CH₃}
\]

as dienophile with anthracene (113):

\[
\text{CHCl} \\
\text{CH-COCH₃}
\]

and as dienophile with cyclopentadiene (114):

\[
\text{CO-R} \\
\text{CO-R}
\]

In the last reaction the chlorine is either exchanged or removed as HCl. Because of the reactivity of the chlorine atom Kochetkov called the introduction of the CH₃COCH = CH-group into a molecule, "Keto-
vinylation”; “ketobutenylation” also occurs in many cases with 1-methoxybutenone (IV), 1-butyn-3-one (VII), or 1-aminobutenone. An example of ketobutenylation with 1-butyn-3-one was carried out by Wenkert and Stevens (115) on 1-methyl-2-naphthol; the following products were obtained:

\[
\begin{align*}
\text{CH}_3 & - \text{OCH} = \text{CH} = \text{C} = \text{CH} - \text{CO} - \text{CH}_3 \\
\text{H}_2 \text{C} & - \text{O} \\
\text{H}_2 \text{C} & - \text{O} \\
\text{little}
\end{align*}
\]

A number of significant syntheses have been carried out with methoxybutenyne (VIII), an important technical starting material for the acetal (I). W. Ried and A. Urschel, in a Merling synthesis, combined VIII with 1,4-cyclohexanediones in liquid ammonia in the presence of lithium amide (116):

\[
\begin{align*}
\text{HO} & - \text{C} = \text{C} - \text{CH} = \text{CH} - \text{OCH}_3 \\
\rightarrow & \\
\text{HO} & - \text{C} = \text{C} - \text{CH} = \text{CH} - \text{OCH}_3 \\
\text{HO} & - \text{C} = \text{C} - \text{CH} = \text{CH} - \text{OCH}_3 \\
\text{HO} & - \text{C} = \text{C} - \text{CH} = \text{CH} - \text{OCH}_3 \\
\end{align*}
\]

The bisbutynal and the bismethoxybutyl compounds were described as secondary products. Corresponding reactions occur with 1,2-dioxocyclohexane; from the substituted 1,2-diol, 1,14-dimethoxy-5,10-dioxotetradecane was obtained with lead tetraacetate. By the reaction of benzoquinone with methoxybutenylene a 20% yield of 1,4-dihydroxy-1,4-bis(4-methoxy-3-buten-1-ynyl)cyclohexadiene-2,5 (117) was obtained, which, on reduction with SnCl\textsubscript{2} in glacial acetic acid, was converted to 1,4-bis(4-methoxy-3-buten-1-ynyl)benzene (118). Only one mole of methoxybutenylene reacts with anthraquinone or with phenanthraquinone (117).

General directions for the addition of methoxybutenylene to dicarbonyl compounds (116) are as follows.

To a liquid ammonia solution containing the calculated amount of sodium is added about 200 mg of finely powdered ferric nitrate. The conversion of sodium is finished when the blue coloring has disappeared. A toluene solution of the methoxybutenylene in then added dropwise. After 30 min the toluene solution of the dicarbonyl compound is added dropwise and the reaction mixture then stirred at \(-35^\circ\) for a whole day. The ammonia is allowed to evaporate overnight, the last traces being removed with a water aspirator. The residue is poured carefully into ice water and immediately neutralized with \(4N\) sulfuric acid. The mixture is fil-
tered and the toluene layer separated. The residue and the toluene solution are washed well with water and then combined. They are heated and purified with activated charcoal. When the toluene solution is concentrated in vacuo the addition product crystallizes.

Marshall and Whitting (119) allowed the Grignard reagent of methoxybutenyne to react with \( p \)-methoxybenzaldehyde to form \( p \)-methoxyphenyl-4-methoxybutenynyl carbinol, whose triple bond was reduced to the double bond with \( \text{LiAlH}_4 \); on acidification the hydroxyl group split off and the enol ether hydrolyzed to form the polyene-aldehyde:

\[
\text{CH}_3\text{O} - \text{C}_6\text{H}_4 - \text{CH} - \text{C} = \text{C} - \text{CH} = \text{CHOCH}_3 \rightarrow \text{CH}_3\text{O} - \text{C}_6\text{H}_4 - \text{CH} - \text{CH} - \text{CH} = \text{CH} - \text{CHO}.
\]

This method, through the reaction of aldehydes, especially unsaturated aldehydes, brings about a lengthening of the carbon chain with four carbon atoms and two double bonds and retention of a terminal aldehyde group.

A solution of 14.6 gm of methoxybutenyne in 20 ml of tetrahydrofuran is added dropwise to a solution of ethylmagnesium bromide (from 3.2 gm Mg) in 90 ml of tetrahydrofuran at 40°. The solution is stirred for 1 hr at 20°, then a solution of 18.1 mg of \( p \)-methoxybenzaldehyde in 20 ml of tetrahydrofuran is added dropwise over a period of 20 min with ice cooling. After stirring at 20° for 2 hr, the solution is cooled to 0°, 5 ml of ethanol added, and after 20 min a total of 4.0 gm of \( \text{LiAlH}_4 \) is added in portions. This mixture is stirred at 20° for 3 hr, then ice cooled and successively treated with 6 ml of ethyl acetate, 30 ml of water, 150 ml of 4\( \text{N} \) sulfuric acid, and 200 ml of ether. After separation of the ether solution and evaporation of the ether, there remains 5-(\( p \)-methoxyphenyl)-2,4-pentadienal which is recrystallized from petroleum ether; m.p. 76-78°, yield 13.1 gm (52%). The pure substance melts at 79-80° (119).

The carbon chain of methoxybutenyne was increased by one carbon by A. Dornow and E. Ische through the reaction of the Grignard compound with orthoformate ester (120) to form 5-methoxy-4-penten-2-yn-1-al acetal (32% yields), from which \( \gamma \)-pyrone may be obtained in 92% yield:

\[
\text{CH}_3\text{OCH} = \text{CH} - \text{C} = \text{C} - \text{CH} = \text{CHOCH}_3 + \text{CH}_3\text{OH}, \text{H}_2\text{O} \xrightarrow{\text{(HgSO}_4)} \text{[(CH}_3\text{O})_2\text{CH} = \text{CH}_2 - \text{C} - \text{C} - \text{CH} = \text{CHOCH}_3] \rightarrow \text{O}
\]
Ten grams of 5-methoxy-4-penten-2-yn-1-al diethyl acetal is dissolved in 20 gm of methanol. Then 1 gm of water and 0.1 gm of mercuric sulfate are added and the mixture stirred for 1 hr at 65°. At the end of the reaction, the mixture is neutralized with soda, filtered, and distilled. There is obtained 4.8 gm (92%) of γ-pyrone, m.p. 31.5° (120).

A lengthening of the methoxybutenyne carbon chain by five carbon atoms is brought about by the reaction with 1-chloro-5-methoxy-1-pentene. The latter is obtained from the reaction of butadiene with chloromethyl methyl ether, the final mixture containing also the isomer, 3-chloro-5-methoxy-1-pentene. The reaction gives a 70% yield of 1,9-dimethoxy-1,6-nonadien-3-yn (120a).

\[
\text{CH}_3\text{O-CH=CH-C≡C-CH}_2\text{-CH-CH}-\text{CH}_2\text{-CH}-\text{OCH}_3 .
\]

By hydrogenation and oxidation pure azelaic acid is obtained.

The Mannich reaction of methoxybutenyne with formaldehyde and dimethylamine gave a 66% yield (121). 1-Methoxy-5-dimethylamino-1,3-pentadiene and 5-dimethylamino-3-pentanonal dimethyl acetal were obtained as end products.

\[
\text{CH}_2\text{O-CH=CH-C≡C-CH}_2\text{-CH-CH-CH-CH}_2\text{-CH}_3\text{N(CH}_3\text{)}_2 \xrightarrow{\text{LiAlH}_4} \text{(CH}_3\text{O)}_2\text{CH-CH}_3\text{-CO-CH}_2\text{-CH}_2\text{-N(CH}_3\text{)}_2 .
\]

The reaction of the Grignard reagent from methoxybutenyne with diethyl carbonate leads to ethyl 5-methoxy-4-penten-2-ynate (122). Methoxybutenyne itself undergoes a reaction, catalyzed by sodium ethoxide, with diethyl carbonate, in which ethanol is added to form \(\text{CH}_3\text{OCH=CHC(OC}_2\text{H}_5\text{)=CHCOOC}_2\text{H}_5\), the bis enol ether of γ-formyl-acetoacetic esters,

\[
\text{OHC-CH}_2\text{-CO-CH}_2\text{-COOR.}
\]

This bis enol ether, after acetalization with ethanol, is transformed to a 1-alkyl-4-amino-2-pyridone by treatment with an amine (122). The condensation of methoxybutenyne with formaldehyde occurs in the presence of caustic alkali and methanol, in which one mole of methanol exothermically adds to the first carbon atom (123).

\[
\text{CH}_3\text{O-CH=CH-C≡C-CH}_2\text{OH} \xrightarrow{} (\text{CH}_3\text{O})_2\text{CH-CH}_2\text{-C≡C-CH}_2\text{OH}
\]

In a flask equipped with a stirrer, 150 gm of solid potassium hydroxide, 400 ml of methanol, and 123 gm of 1-methoxy-1-butene-3-yn are heated to 50-55° and then 135 gm of paraformaldehyde is added over a period of 3 hr at the temperature indicated. When the reaction is finished the solution is cooled and neutralized with formic acid. The excess
methanol is removed by using a slight vacuum and warming, until potassium formate begins to precipitate in the aqueous layer. The mixture is extracted with ether; the ether extracts are dried. Methoxybutenyne and butynal acetal are distilled off, leaving as a residue 1-methoxy-1-penten-3-yn-5-ol, which boils at 130–133°C/22 mm. The yield is over 65%, based on methoxybutenyne.

A mixture of 120 gm of 1-methoxy-1-penten-3-yn-5-ol, 250 ml methanol and 300 gm of caustic alkali is stirred at 60°C for 4 hr; after this period the mixture is cooled and neutralized with formic acid, layers being formed. The upper layer (233 gm) is distilled. There is obtained 81 gm of 3-pentyn-5-ol-1-al dimethyl acetal, b.p. 90–110°C/1.2 mm. The yield is 65%, based on methoxypentenynol.

Hydration in methanol leads to 5-methoxy-3-pentan-1-ol dimethyl acetal (124).

\[
\text{CH}_3\text{O—CH—CH—CO—CH—CH(OCH}_3)\text{_2.}
\]

Starting with 5-hydroxy-3-pentynal dimethyl acetal, F. Weygand and H. Leube found a new approach to deoxyribose (125):

\[
\begin{array}{c}
\text{H}_3\text{Pd} \\
\text{(Pb)}
\end{array}
\rightarrow
\begin{array}{c}
\text{CH}_3\text{OH} \\
\text{CH}_2\text{OH}
\end{array}
\]  

\[
\begin{array}{c}
\text{CH}_3\text{O} \\
\text{OH}
\end{array}
\]  

The synthesis of very pure suberic dialdehyde is brought about by the oxidation of methoxybutenyne with oxygen in the presence of cuprous salts and pyridine (126) to form:

\[
\text{(CH}_3\text{O)—CH=CH—C=C—)}\text{H}_2.
\]

followed by the addition of two moles of methanol to give the 1,8-bisdimethyl acetal, followed by hydrogenation to suberic dialdehyde bisacetal and hydrolysis to the final product (127).

Starting with methoxybutenyne, O. Westphal and E. Rüde (Erwin Rüde, Dissertation, Univ. Freiberg/Brsg., 1960) synthesized 3,6-dideoxyhexoses, which had been found as a natural component in bacterial antigens (128).

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