Synthesis and Reactions of Glutaconaldehyde and 5-Amino-2,4-pentadienals

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The structure, preparation, and reactions of glutaconaldehyde (5-hydroxy-2,4-pentadienal) and 5-amino-2,4-pentadienal are reviewed.

1. Introduction

This review deals with the structure and chemistry of glutaconaldehyde (1; 5-hydroxy-2,4-pentadienal), which has only received sporadic attention in the past. Due to its instability even in solution, the free glutaconaldehyde (1) has never been isolated; however, stable glutaconaldehyde salts of type 2 have been known1 since 1924, when the first salt of this anion, the sodium dihydrate, was described.

![Structure 1](image1)

![Structure 2](image2)

2. Structure of Glutaconaldehyde and Derivatives

The structures of the O-acylated glutaconaldehyde derivatives have been investigated in detail2,3,4,5. These investigations confirmed that these compounds have the all-trans structure as shown for the enol ester 3.

![Structure 3](image3)

However, in some cases glutaconaldehyde derivatives with cis-structure have been reported. Most of these are primary products from pyridine ring openings6 in which a cis-arrangement of the double bond to the imino nitrogen has been preserved. As the cis- and trans-coupling constants in the 1H-N.M.R. spectra of many glutaconaldehyde derivatives are of the same order of magnitude, the assignments of structure on the basis of these spectra are only clear-cut in the cases where both cis- and trans-isomers have been isolated. It must be pointed out that in most cases glutaconaldehyde derivatives have the thermodynamically stable all-trans structure, contrary to the all-cis structures usually depicted in textbooks. Recently a glutaconaldehyde enol ester with a cis-double bond has been isolated7.

3. Synthesis of Glutaconaldehyde

3.1. Free Glutaconaldehyde

The free glutaconaldehyde (5-hydroxy-2,4-pentadienal; 1) can be prepared in solution according to the following scheme8.

![Scheme 4](image4)
Methanolic Solution of Glutaconaldehyde (1)\textsuperscript{11}:
To a solution of 4 (0.1 g, 0.64 mmol) in methanol (2 ml) is added an excess of solid carbon dioxide (~10 g). The cold solution is filtered as quickly as possible. This solution of 1 is stable for ~30 min at ~70°C. The free glutaldehyde may be extracted into ether from an acidified solution of protonated glutaldehyde\textsuperscript{11}.

3.2. Glutaconaldehyde Salts 2

Since Baumgarten's first paper\textsuperscript{1}, glutaldehyde has been mentioned many times in the literature without reliable experimental details. However, a reproducible method for the preparation of salts of glutaldehyde has recently been published\textsuperscript{11}.

\[ \text{NaOH, \text{-20°C}} \rightarrow [\text{\begin{array}{c} \text{N-SO}_3^- \\ \text{H} \end{array}}]_2 \text{Na}^+ \quad \text{(5)} \]

\[ \text{Na}^+ \cdot 2 \text{H}_2\text{O} \quad \text{(4)} \]

Yields of analytically pure sodium salt dihydrate (4) or the anhydrous potassium salt are 58%. The disodium salt 5 may be isolated in 93% yield. In Table 1 some useful properties of these salts are summarised.

Table 1. Some Properties of Glutaconaldehyde Salts

<table>
<thead>
<tr>
<th>Cation</th>
<th>Molecular formula</th>
<th>Yield [%]</th>
<th>m.p. [°C]</th>
<th>Solubility at 20°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na\textsuperscript{+}, 2H\textsubscript{2}O</td>
<td>C\textsubscript{6}H\textsubscript{4}NaO\textsubscript{4} \textsubscript{(156.1)}</td>
<td>58</td>
<td>&gt;350\superscript{a}</td>
<td>H\textsubscript{2}O (8.2 g/100 ml); CH\textsubscript{3}OH (11.5 g/100 ml); DMF (7.2 g/100 ml); DMSO (25.4 g/100 ml) pyridine</td>
</tr>
<tr>
<td>K\textsuperscript{+}</td>
<td>C\textsubscript{6}H\textsubscript{4}K\textsubscript{2}O \textsubscript{(136.2)}</td>
<td>58</td>
<td>&gt;350\superscript{a}</td>
<td>H\textsubscript{2}O; CH\textsubscript{3}OH; DMSO; DMF</td>
</tr>
<tr>
<td>(\text{\text{\text{-}C\textsubscript{6}H\textsubscript{4}}}\text{\text{-N\textsuperscript{+}, \text{-H\textsubscript{2}}O)}</td>
<td>C\textsubscript{6}H\textsubscript{4}K\textsubscript{2}O \textsubscript{(357.6)}</td>
<td>74</td>
<td>105-108\superscript{a}</td>
<td>C\textsubscript{6}H\textsubscript{4}OAc; C\textsubscript{6}H\textsubscript{4}CH\textsubscript{2}Cl;</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Water solutions of these salts are stable when the pH is adjusted to pH > 12. Solutions in non-hydroxylic solvents such as dimethyl sulfoxide and dimethyl formamide are stable without addition of base\textsuperscript{14}.

Another synthesis for the glutaldehyde potassium or sodium salts involves\textsuperscript{11} the hydrolysis of the imine 6 using potassium or sodium hydroxide.

\[ \text{C\textsubscript{6}H\textsubscript{4}N-\text{\text{\text{-}CH\textsubscript{3}}} \rightarrow 2 \text{Na}^+ / \text{H}_2\text{O} \rightarrow 2 \text{C\textsubscript{6}H\textsubscript{4}N-\text{\text{-}CH\textsubscript{3}}} \text{H}_2\text{O} \rightarrow 2 \text{C\textsubscript{6}H\textsubscript{4}N-\text{\text{-}CH\textsubscript{3}}} \text{H}_2\text{O} \text{Na}^+ \cdot 2 \text{H}_2\text{O} \text{Na}^+ \cdot 2 \text{H}_2\text{O} } \]

Glutaconaldehyde Sodium Salt Dihydrate (4)\textsuperscript{11}:
5-N-Methylaminopenta-2,4-dienylidene-1-N-methylamininium chloride\textsuperscript{12} (6.32 g, 0.1 mol) is dissolved in methanol (200 ml) and a solution of sodium hydroxide (40 g, 1 mol) in water (200 ml) is added. The mixture is heated at 60-70°C for 2-5 min and cooled, whereupon the separated glutaldehyde sodium salt dihydrate (4) is collected as yellow needles; yield: 11.2 g (90%). The potassium salt can be obtained by an analogous method.

Glutaconaldehyde salts 2 have also been obtained from derivatives such as the diacetals 7, by acidic hydrolysis followed by the addition of sodium hydroxide; the yields in these reactions are usually low.

\[ \begin{array}{c}
\text{C}_2\text{H}_5\text{O} \\
\text{O} \\
\text{C}_2\text{H}_5\text{O} \\
\text{O} \\
\text{C}_2\text{H}_5\text{O} \\
\text{O} \\
\text{C}_2\text{H}_5\text{O} \\
\text{O} \\
\end{array} \rightarrow \begin{array}{c}
\text{H} \\
\text{O} \\
\text{C}_2\text{H}_5\text{O} \\
\text{O} \\
\text{C}_2\text{H}_5\text{O} \\
\text{O} \\
\text{C}_2\text{H}_5\text{O} \\
\text{O} \\
\end{array} \\
\text{Na}^+ \\
\text{H}_2\text{O} \\
\text{H}_2\text{O} \\
\text{H}_2\text{O} \\
\text{H}_2\text{O} \\
\text{H}_2\text{O} \\
\text{H}_2\text{O} \\
\text{H}_2\text{O} \\
\end{array} \]

However, this method has been used for obtaining alkyl substituted aldehyde derivatives in fair yields\textsuperscript{13}.

Glutaconaldehyde Sodium Salt Dihydrate (4)\textsuperscript{11}:
A mixture of 1,1,3,5,5-pentachloropentane (7; 11.7 g, 0.04 mol) in 1 molar hydrochloric acid (10 ml) is shaken at 30°C until a homogeneous solution results. After 10 min at room temperature 5 molar sodium hydroxide (10 ml) is added. The mixture is cooled and the precipitated crystals isolated and washed with ice/water; yield of crude product: 2.65 g (55%).

4. Reactions of Glutaconaldehyde Salts

4.1. Acyclic Derivatives

Compounds which are directly related to the glutaldehyde salts 2 or the enol esters 3 will be discussed.

4.1.1. O-Acetylation

Hard acids such as acid chlorides, acid anhydrides, phenacyl bromides, and acyl isothiocyanates react at the enolate site of salts 2, which is a hard base\textsuperscript{15}, to give the corresponding enol esters 3 or in the case of the phenacyl bromide, the corresponding ether 8. The derivatives 3 and 8 are usually stable, but, as enol ethers or esters, they are readily hydrolysed\textsuperscript{4} yielding the free glutaldehyde.
5-Hydroxy-trans-2,trans-4-pentadienal Benzoate\(^ {3,15,17}\)  
\( R = C_6H_4 \)

Glutaconaldehyde sodium salt dihydrate (4; 6 g, 39 mmol) is stirred in pyridine (12 ml) at 0 °C. Benzyl chloride (8 g, 57 mmol) is slowly added. The mixture is stirred for another 5 min, cooled to 0 °C, and water (100 ml) is added to give, after filtration, the enol ester as cream-coloured needles, yield: 8.9 g (94%); m.p. 116–118 °C. Recrystallisation from 96% ethanol (with activated carbon) yields colourless needles; m.p. 120–121 °C.

Alternative procedures from the acyl isothiocyanates are given in Refs.\(^ {7,16}\).

As seen from Table 2, these derivatives are usually obtained in good yields and may be used as a source of the all-trans pentadiene system.

**Table 2. Selected 5-Hydroxy-trans-2,trans-4-pentadienal Esters 3**

<table>
<thead>
<tr>
<th>Ester 3</th>
<th>Yield [%]</th>
<th>m.p. [°C]</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>H(_2)C(\text{--CO-CH}_2\text{-O--CO-CH}_2\text{-O})</td>
<td>90</td>
<td>76–77(^{9})</td>
<td>1, 2</td>
</tr>
<tr>
<td>H(_2)CO(\text{--CO-CH}_2\text{-O--CO-CH}_2\text{-O})</td>
<td>91</td>
<td>119–120(^{9})</td>
<td>13</td>
</tr>
<tr>
<td>C(_2)H(_5)CO(\text{--CO-CH}_2\text{-O--CO-CH}_2\text{-O})</td>
<td>74</td>
<td>67–69(^{8})</td>
<td>15, 16</td>
</tr>
<tr>
<td>C(_6)H(_5)CO(\text{--CO-CH}_2\text{-O--CO-CH}_2\text{-O})</td>
<td>94</td>
<td>120–121(^{9})</td>
<td>1, 2, 17</td>
</tr>
<tr>
<td>Br(\text{--CO-CH}_2\text{-O--CO-CH}_2\text{-O})</td>
<td>92</td>
<td>161–163(^{8})</td>
<td>=</td>
</tr>
<tr>
<td>C(_6)H(_5)CO(\text{--CO-CH}_2\text{-O--CO-CH}_2\text{-O})</td>
<td>7</td>
<td>103–105(^{8})</td>
<td>5</td>
</tr>
<tr>
<td>C(_6)H(_5)CO(\text{--CO-CH}_2\text{-O--CO-CH}_2\text{-O})</td>
<td>61</td>
<td>138–139(^{8})</td>
<td>5</td>
</tr>
<tr>
<td>C(_6)H(_5)CO(\text{--CO-CH}_2\text{-O--CO-CH}_2\text{-O})</td>
<td>61</td>
<td>113–116(^{8})</td>
<td>18</td>
</tr>
</tbody>
</table>

\(^{\ast}\) J. Becker, unpublished results.

**Sodium Salt of 2-Bromo-5-hydroxy-trans-2,trans-4-pentadienal Diacid (9; X = Br):**

The glutaconaldehyde sodium salt (4; 6.24 g, 0.04 mol) is dissolved in water (200 ml, 0 °C), and bromine (1.7 ml, 0.03 mol) is added under vigorous stirring. The red-orange mixture is stirred for 5 min and then extracted with ether (4 × 300 ml). The yellow ether phase is dried with sodium sulfate and concentrated (100 ml) in vacuo. To the cooled ether phase is subsequently slowly added a 0.5 molar methanolic solution of sodium hydroxide (16 ml), whereupon the pH of the solution is raised to 3.5 to 9.6. The precipitated light brown sodium salt is filtered, washed with dry ether, and dried; yield: 8.0 g (70%); m.p. > 100 °C (dec).

This crude product, which is a dihydrate, is pure enough for most preparations and may be purified by recrystallising in methanol with activated carbon (1 g salt/20 ml of methanol) for 3 h. The hot mixture is filtered whereupon addition of dry ether precipitates the pure salt. [A table of halogen substituted 5-hydroxy-2,4-pentadienal esters can be found in Refs.\(^ {8,11}\)].

The salts 9 or 10 were easily acylated to give the corresponding all-trans enol esters, 11 or 12, respectively. When benzyl chloride was used, the reactions with the mono halo-salt 9 were regio-specific to give only the C-2 halo-isomer, whereas the reaction with ethyl carbonochloridate yielded a 1:3 mixture of the two possible isomers, 14 and 15. Bromination\(^ {5}\) of the benzoate 3 was also regio-specific and gave exclusively 13 (X = Br).
A similar regio-specific reaction, corresponding to the benzoylation reaction in pyridine of the salt 9, was found in the benzoylation reactions of the imine salts 17, obtained from the ring opening of 3-substituted pyridines 16.

When the 2-methyl-substituted sodium salt 19 was benzoylated the expected 1:1 mixture of the two possible isomers, 20 and 21, was obtained.

The unstable 2-iodo-substituted glutaconaldehyde 22 can be prepared from the glutaconaldehyde potassium salt.

5-Hydroxy-2-iodo-trans-2, trans-4-pentadienal (22): Glutaconaldehyde potassium salt (1.36 g, 0.01 mol) is dissolved in ice-cold water (25 ml). A solution of potassium triiodide (2 g iodine and 16 g potassium iodide in 25 ml of water) is added with stirring while the temperature is maintained at 0°C by addition of ice. The resulting orange suspension is extracted rapidly with ether (2 x 125 ml). This extract is dried with sodium sulfate, activated carbon is added, the mixture is filtered, and the solvent is evaporated in vacuo (bath temp. < 20°C). The last traces of solvent are removed under high vacuum (~ 1 torr) to give the title compound as unstable orange-tan coloured crystals; yield: 0.92 g (41%); m.p. 90°C.

The substitution reactions of amino derivatives of glutaconaldehyde are related to those of the parent glutaconaldehyde salts, as was found in the facile formylation of the salt 24 to give the 4-formyl-substituted aminoaldehyde 25. Later Kuchera and Arnold also reported that 24 was easily substituted at C-2 to give 26.
A review of the electrophilic and nucleophilic substitution reactions in vinamidinium salts such as

\[
\text{(H}_3\text{Cl})_2\text{N}^+\text{C} \equiv \text{C} \text{CH}_2\text{N(CH}_3)_2\text{C}^{-}
\]

has recently appeared\(^{22}\).

4.1.3. Extension of the Carbon Chain

A number of methods for chain extension have been used in the glutaconaldehyde series. Malhotra and Whiting\(^{14}\) used the reaction of the Zincke aldehyde 27 with phenylethynylmagnesium bromide to give 28 upon hydrolysis. The same reaction sequence with ethynylmagnesium bromide gave 29 in fair yield, from which the vinylether 30 was obtained. Compound 31 finally gave the salt 32 upon hydrolysis.

A large number of unsaturated alkoxyacetals with nine carbon atoms or more in the chain, can be obtained by this method starting from the glutaconaldehyde acetalts 34. The Wittig reaction may also be used\(^{27}\) for the aldehyde group in the glutaconaldehyde benzoyl ester, however, product yields are only moderate.

\[
\begin{align*}
\text{C}_8\text{H}_5\text{-COO} & \quad \text{C}_2\text{H}_5
\text{H} & \quad \text{C}_2\text{H}_5
\text{P}-\text{CH}_2-\text{COOC}_2\text{H}_5
\hline
3 & 36 & 37
\end{align*}
\]

The Vilsmeier-Haack reaction was used\(^{25}\) on the 5-aminopentadienal 38, to give the aldehyde 39. It was

\[
\begin{align*}
\text{C}_8\text{H}_5\text{-C} \equiv \text{C} \text{CH}_2\text{N(CH}_3)_2\text{C}^{-}
\hline
30
\end{align*}
\]

A chain extension via glutaconaldehyde acetalts has been studied\(^{23}\). The acetalts (prepared from 2,6-di-alkoxy-\(\Delta^1\)-dihydropyrans) were condensed with vinyl and propenyl alkyl ethers\(^{24}\).

\[
\begin{align*}
\text{R}^1\text{O} & \quad \text{R}^1\text{O}
\text{OR}^1 & \quad \text{OR}^1
\text{R}^1\text{O} \quad \text{R}^2-\text{CH} \equiv \text{CH} \quad \text{OR}^1
\text{ZnCl}_2
\hline
33 & 34 & 35
\end{align*}
\]

also reported\(^{26}\) that a Grignard reaction could transform 38 into the aldehydes 40 in reasonable yields (38–60%).

This reaction has been used\(^{27}\) for the preparation of related imine salts 41.

The hydroxy group in glutaconaldehyde salts may be substituted by chlorine to afford 42\(^{28}\).
be conveniently obtained 95% pure by a modified procedure\(^5,30\).

The acetals 43–46 as well as the corresponding cyclic acetals\(^{31}\) can be obtained by other routes. From the cyclic acetal 47, acetals of glutaraldehyde can be obtained by hydrolysis\(^{31}\).

If catalytic amounts of boron trifluoride etherate are used\(^1\) for the hydrolysis, the glutaraldehyde dimethyl acetics 48 are obtained directly.

Halogen-substituted glutaraldehyde acetals have also been prepared\(^{311}\).

On the basis of the above described reactions, the following scheme outlines the syntheses of reduced glutaraldehyde derivatives.

---

5-Chloro-trans-2,trans-4-pentadienal (42):\(^5\)

The glutaraldehyde sodium salt 4 in ether at -20 °C is treated with an excess of phosphene at -20 °C. The reaction mixture is subsequently stirred at room temperature for 1.5 h. Filtration, washing of the filtrate with ether, evaporation, and sublimation followed by recrystallisation afford compound 42; yield: 55%; m.p. 57 °C.

4.1.4. Reduced Derivatives. Acetals

The glutaraldehyde acetals may be prepared directly from glutaraldehyde salts\(^5\). The following acetals can be obtained from glutaraldehyde salts upon treatment with methanolic hydrogen chloride\(^5\).

Glutaraldehyde Dimethyl Acetal (43):\(^5,7\)

Glutaraldehyde sodium salt dihydrate (4, 20 g, 0.13 mol) and dry methanol (50 ml) are stirred with 8.2 molar methanolic hydrogen chloride (22.3 ml) for 14 h at room temperature. The reaction mixture is then mixed with an ice-cold saturated calcium chloride solution (130 ml). further ice (20 g) is added, and after 20 min the mixture is extracted with ether. The ether phase is washed with water, dried with potassium carbonate, and distilled. The acetal 43 is obtained as an oil; yield: 6 g (28%); b.p. 99–103 °C/16 torr; n\(_D\)\(^20\) 1.4220.

However, the most stable acetal is the synthetically useful pentamethoxy derivative 46. This product can...
The parent compound in some of these transformations, 3-hydroxy-1,5-pentanedione (49) was prepared under mild conditions by two methods, however no experimental details were given. This di-aldehyde is stable for some days in water under neutral conditions.

It is possible to prepare glutaraldehyde acetals from glutaraldehyde acetals.

Partial hydrolysis of these acetals is possible. Hydrolysis of the pentaalkoxypentane (e.g. 50) in dilute phosphoric acid gives the dialdehyde 52 as the main product, with the cyclic acetal 51 as a byproduct. Hydrolysis in hydrochloric acid gives the dialdehyde as the main product.

Phosphoric acid hydrolysis of the glutaraldehyde diethyl acetal (54) as the main product.
4.2. Carboxyclic Compounds

4.2.1. Azulenes

Glutaconaldehyde enol esters do not undergo Diels-Alder reactions easily\textsuperscript{17}, while the elegant use of glutaconaldehyde derivatives for the preparation of azulenes is well documented\textsuperscript{19}. The fulvene 55 obtained in high yield from the aminopentadienal 27 and cyclopentadiene could be cyclized to azulene 56 in fair yield.

\[
\begin{align*}
\text{C}_6\text{H}_5\text{NH}=\text{CHCH=CHCH}_2\text{H} + \text{C}_5\text{H}_4 & \xrightarrow{\Delta, 200-300 \, ^\circ\text{C}} \text{C}_6\text{H}_5\text{NN}=\text{CCH=CHCH}_2\text{H} \\
\end{align*}
\]

Also, substituted fulvenes have been used to give azulenes with substituents on the 5-ring. In order to obtain substituted azapolyenaldehydes for the preparation of azulenes substituted in the 7-ring, a number of substituted glutaconaldehyde derivatives of the 5-aminopentadienal type have been prepared\textsuperscript{10}.

4.3. Heterocyclic Compounds

4.3.1. Pyridine

The most simple preparation of pyridine is the ring closure of a glutaconaldehyde salt with ammonium acetate.

\[
\begin{align*}
\text{O}=\text{CCH} & \xrightarrow{\text{H}_3\text{CCOO}\text{NH}_2} \text{pyridine} \\
\end{align*}
\]

This method has been used\textsuperscript{41} for the preparation of \textsuperscript{15}N-pyridine. The preparation of pyridines\textsuperscript{42} from glutaconaldehyde salts are summarised in Table 3.

### Table 3. Pyridines from Glutaconaldehyde Derivatives

<table>
<thead>
<tr>
<th>Glutaconaldehyde Salt</th>
<th>Reagent</th>
<th>Product</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>[\text{O}=\text{CCH}\text{Na}^+\cdot 2 \text{H}_2\text{O}]</td>
<td>[\text{NH}_2\text{COOH}\cdot \text{H}_2\text{O}^\oplus]</td>
<td>[\text{pyridine}]</td>
<td>1</td>
</tr>
<tr>
<td>[\text{O}=\text{CCH}\text{Na}^+]</td>
<td>[\text{NH}_2\text{H}_3\text{PO}_4]</td>
<td>[\text{pyridine}]</td>
<td>41</td>
</tr>
<tr>
<td>[\text{O}=\text{CCH}\text{Na}^+\cdot 3 \text{H}_2\text{O}]</td>
<td>[\text{NH}_2\text{H}_3\text{PO}_4]</td>
<td>[\text{pyridine}]</td>
<td>43, 44, 45</td>
</tr>
<tr>
<td>[\text{O}=\text{CCH}\text{Na}^+]</td>
<td>[\text{NH}_2\text{COOH}\cdot \text{H}_2\text{O}^\oplus]</td>
<td>[\text{pyridine}]</td>
<td>8, 45</td>
</tr>
<tr>
<td>[\text{O}=\text{CCH}\text{Na}^+]</td>
<td>[\text{NH}_2\text{COOH}\cdot \text{H}_2\text{O}^\oplus]</td>
<td>[\text{pyridine}]</td>
<td>46</td>
</tr>
</tbody>
</table>

The stable imine salts 57 of glutaconaldehyde have often been used for the preparation of pyridines, for example in the preparation of \textsuperscript{29}N-arylpuridinium salts\textsuperscript{29, 47, 48}. The cyclisations of azatrienes have been reviewed\textsuperscript{69}. The glutaconaldehyde acetics also react with ammonia to give pyridines\textsuperscript{69}.

Pyridine \(N\)-oxide was prepared from the glutaconaldehyde oxime under acidic reaction conditions\textsuperscript{50}, the following scheme outlines these reactions: (see Ref.\textsuperscript{64} for an explanation of the 1,2-oxazoline reaction).
Tamura et al.\textsuperscript{50} conclude that the most convenient method is from the 2,4-dinitrophenylpyridinium chloride directly.

**Pyridine N-Oxide (59)\textsuperscript{51}:**
An ice-cooled solution of hydroxylamine hydrochloride (1.39 g, 0.02 mol) and sodium hydroxide (0.8 g, 0.02 mol) in water (8 ml) is added dropwise to 2,4-dinitrophenylpyridinium chloride (2.82 g, 0.01 mol) and then dioxan (30 ml) is added to the mixture. The mixture is heated under reflux for 5 h. Concentration in vacuo and addition of water (40 ml) gives 2,4-dinitroaniline (1.70 g) which is filtered. The filtrate is concentrated in vacuo, dissolved in chloroform (20 ml), and dried with potassium carbonate. Distillation gives pyridine N-oxide; yield: 0.45 g (50%); b.p. 136–140 °C/15 torr. The product solidifies upon standing (m.p. 62–65 °C).

This method can be used for the preparation of 2- and 3-picoline N-oxides as well as for 3,5-lutidine N-oxide and gives fair yields.

Also N-aminopyridinium chlorides 62 can be prepared from 2,4-dinitrophenylpyridinium chloride\textsuperscript{50}.

A related synthesis of 62 from pyrrolium salts has been reported\textsuperscript{31}.

4.3.2. Pyrrolium Salts

It is known\textsuperscript{30} that pyrrolium salts react with the hydroxide ion, giving rise to ring-opened products, which in fact are glutaconaldehydes.

4.3.3. Pyridones, Thiones and Selenones

Glutaconaldehyde salts react\textsuperscript{55–59} with heterocumulenes i.e. organic isocyanates, isothiocyanates, and isoselenocyanates in solvents such as dimethyl sulfoxide or dimethylformamide, to give 1-substituted-3-formyl-2(1H)-pyrroles, -thiones, and -selenones, respectively.
$^{13}$C- and $^1$H-N.M.R. spectroscopic studies showed that stable intermediate salts 64 were formed. The cyclisation step leading to the products only takes place in the presence of water$^{37}$.

1-Aryl-3-formyl-2(1H)-pyridinedithione 65 (R = aryl); General Procedure:
The sodium or potassium salt of glutaraldehyde (0.01 mol) in dimethyl sulfoxide or dimethylformamide (10 ml) and the aryl isothiocyanate (0.01 mol) are stirred at room temperature for 2 h. Addition of the dark reaction mixture to water (100 ml) and stirring for some minutes gives the product as orange crystals, which are dried and recrystallized.

For the preparation of the corresponding $N$-alkyl analogues, the reaction mixture must be heated and the product extracted from the resulting solution.

The thione 65 with R = $t$-butyl gives the parent thione (R = H) in quantitative yield$^{54}$ on pyrolysis.

Cyclisation of the intermediates 64$a$ and 64$b$ from ring-opening reactions of nicotinamide derivatives are known$^{60,61}$. These reactions resemble those of the stable intermediate 64 with water.

A derivative 67 also resembling the intermediates 64 has been isolated$^{62}$.

4.3.4. Other Heterocyclic Compounds

Thiophenes: The reaction of the sodium salt of chloroglutaraldehyde with hydrogen sulfide gives thiophene-2-carboxaldehyde (68) in low yield$^{63}$.

4,5-Dihydro-1,2-oxazole: The reaction product from glutaraldehyde salts and hydroxylamine has recently been shown$^{64}$ to be the 4,5-dihydro-1,2-oxazole 69.

5. Nucleophilic Ring Opening Reactions of Pyridinium Salts

The nucleophilic ring opening reactions of pyridinium compounds have been reviewed$^{65}$. Therefore, only examples in which these reactions result in the actual isolation and identification of a ring opened product are included here. The many examples in which pyridinium compounds give rise to glutaraldehyde derivatives and the cases in which the pyridinium system does not ring open will be not discussed.

The most important condition for a successful pyridine ring opening is the presence of an electrophilic substituent at the pyridine nitrogen as shown in the following examples.
The next prerequisite is to have a strong nucleophile such as the hydroxide ion in concentrated sodium hydroxide, or in sodium carbonate solution, albeit the cation may also have a small influence\(^\text{60}\). The relation between the yields of ring-opened product and the ionic radius of the cation was determined and the relation lithium hydroxide < sodium hydroxide < potassium hydroxide corresponding to the yields 67%, 69%, and 74% found.

Nucleophiles other than hydroxide ion have been used. Reactions with compounds containing active methylene groups, as shown below, and other reagents must be carried out in the presence of a base such as hydroxide, cyanide, or an amine to promote opening of the pyridine ring, whereupon the glutaraldehyde reacts with the active methylene group (see Section 6.3.).

A base such as ammonia can also cause ring opening of pyridinium compounds\(^\text{67}\), but unstable products are usually formed.

The influence that the ring carbon substituents have for the ring opening of the pyridines should be mentioned. Most ring opening reactions have been performed with the unsubstituted pyridine. The pyridine ring-opening reaction always takes place at the carbon atom next to nitrogen; the ring, therefore, must be unsubstituted at one of these positions. An electronegative substituent at C-3, such as nitrile > carboxylic acid > chloride > amide promotes\(^\text{60}\) ring opening in the pyridine N-oxide series, the substituent is preferred at C-3 > C-2 > C-4, in this series. Unsubstituted, alkyl-substituted, as well as C-2 and C-4 chloro-substituted pyridines do not react.

For the classical ring opening reactions, the Baumgarten, König, or Zincke openings, Hafner and Asmus\(^\text{40}\) found that reaction with cyanogen bromide and aniline gave a lower yield for 2- or 4-methylpyridine and a higher yield for 3-methylpyridine as well as 3-chloropyridine, while the 2-chloro, 2-methoxy, 2-formyl, 3-carboxy and 3-(2-propenyl) derivatives did not react under these conditions.

Ring openings of 2-methyl, 4-methyl, 2,4,6-trimethyl-, 3-bromo-, and 3-phenylpyridinium 1-sulfonates do not take place using the Baumgarten method. Likewise, 3-bromo-, 3-chloro-, 4-methyl-, 3,5-dimethyl-, and 4-4-butylpyridinium 1-sulfonates could not be ring opened under these reaction conditions, while 3-methyl- and 3-methoxypyridinium-1-sulfonates were ring opened to give glutaraldehyde derivatives in good yields. These ring openings were specific, taking place at C-2.

The important 5-amino-3-methyl-2,4-pentadienal was prepared in fair yield by the König method from 4-methyl-1-(2,4-dinitrophenyl)-pyridinium chloride\(^\text{68}\).

Thus, it has been concluded\(^\text{70}\) from substituent effects in the pyridine series that the C-2 position is attacked preferently by nucleophiles. Hard bases give reaction at C-2 while soft bases prefer reactions at C-4 for example in the reaction of cyanide ion with nicotinamide\(^\text{71}\). Therefore, we can conclude, from the many examples in Table 4, as well as from the previous examples that the ring opening of a 3-substituted pyridine \(70\) is often a regioselective reaction\(^\text{72}\) which yields the corresponding 2-substituted-5-amino-2,4-pentadienal \(71\).

In order to include these ring opening reactions in a common reaction scheme, an intermediate such as \(73\) has to be postulated in the pericyclic process leading to ring opening, in some cases stable intermediates of type \(73\) have been isolated\(^\text{93}\).

The problem of pseudo base formation in the pyridine series has been reviewed\(^\text{73}\). Originally the existence of a true equilibrium, when a quaternary base such as a 1-substituted pyridinium compound is attacked by base, was postulated\(^\text{74}\). Enols such as \(76\) are usually unstable, but can be isolated as their enol esters. From this scheme we can conclude that in aqueous solution the quaternary heteroaromatic ion reacts with a hydroxide ion to yield an adduct (pseudo base). The formation of this adduct depends on the type of substituents on the nitrogen and in the ring. An electron-withdrawing substituent on nitrogen or simultaneous reactions with electrophilic reagents often gives rise to an open aminoaldehyde de-
6. **5-Amino-2,4-pentadienals**

6.1. **Structure and Reactions**

The parent 5-amino-2,4-pentadienal, *N*-substituted, *N,N*-disubstituted derivatives (Zincke aldehydes), the corresponding salts, and enol ethers and enol esters are discussed (see Table 4). The corresponding imides and their salts are only mentioned as starting materials as they have been reviewed recently. The structure, spectra, nature of the bonds, and the electron distribution in these compounds, e.g., **80**, have been extensively studied. Dahme et al. have given a scheme in which the additional resonance energies of polyunsaturated compounds are compared, here the 5-amino-2,4-pentadienals are found to have values between the fully aromatic molecules and simple polyenes, while the cyanines have values close to the values of aromatic compounds.

The polarisability of the *π*-electrons in the 5-amino-2,4-pentadienals is reflected in the high dipole moments found in these compounds. The U.V. spectrum of the parent 5-amino-2,4-pentadienal ion showed an absorption at $\lambda_{\text{max}} = 360$ nm in alkaline solution. For the *N*-mono- and *N,N*-disubstituted 5-amino-2,4-pentadienals, representative spectroscopic values are reported. For the crystalline derivative, an X-ray investigation was recently performed, which confirmed the previously assigned all-trans structure.

It can be concluded that the mesomers with high electron density at C-2 and C-4 are also important. These resonance structures correspond well to the scheme suggested for the glutaraldehyde anion.
It must be remembered that it is not uncommon that many of the more or less unstable primary products isolated from pyridine ring openings are obtained with cis configuration most often for the double bond next to the nitrogen atom (the former pyridine nitrogen – see Ref.112). The 5-amino-2,4-pentadienals are usually stable in base and in some cases salts such as 83 have been identified25a, b.

From the stable aldehyde 84, the salt 85 is formed28 in methanolic potassium hydroxide. Although this salt could not be isolated; the sodium salt 86 has been isolated29 from the reaction of the corresponding pyridinium salt and sodium hydroxide.

In this connection it is interesting that the amino-2,4-pentadienals can be O-acylated30 to give the salt 88, stable under anhydrous conditions31. Some reactions of the 5-amino-2,4-pentadienals have already been mentioned (cf. Section 4.), while the reactions with compounds containing active methylene groups are referred to in Section 6.3.

Finally the photochemical ring opening of pyridine N-oxide should be mentioned. Unsaturated nitriles can32 be obtained by irradiation of pyridine N-oxide in the presence of secondary amines. Recently33 this reaction has been demonstrated to be general, leading to new and interesting polyenes, e.g. 92.

One of these nitriles was identified by independent synthesis from the Zincke aldehyde, via the oxime.

6.2. Preparation

According to the classical ring opening of pyridine92, the N-(2,4-dinitrophenyl)-pyridinium chloride (94) is ring opened by treatment with sodium carbonate, to give the perfectly stable red coloured aldehyde 95. The N-(2,4-dinitrophenyl)-pyridinium chloride (94) is an important synthon for the preparation of 5-amino-2,4-pentadienals, and can be prepared in almost quantitative yield. The aldehyde 95 has the all-trans-structure50.

N-(2,4-Dinitrophenyl)-pyridinium Chloride (94)50:
2,4-Dinitrochlorobenzene (100 g, 0.49 mol) is dissolved in pyridine (80 g, 1.01 mol), and heated on a steam bath with stirring until the yellow solution darkens (~ 1 h). The heating is stopped, and with-
in a short time an exothermic crystallisation starts. After cooling, the product is filtered, washed with ether and, recrystallised from ethanol, to give colourless crystals of 94; yield 127 g (90%); m.p. 190–191 °C. This reaction is more easy to control when acetone (500 ml) is used as solvent. The mixture is refluxed for 1 h with stirring and cooled, whereupon the precipitated product can be filtered and washed with pentane.

5-(2,4-Dinitroanilino)-trans-2,trans-4-pentadienal (95)\[24\]:
N-(2,4-Dinitrophenyl)-pyridinium chloride (94) is dissolved in water (10 ml/1 g of chloride), whereupon 0.2 molar sodium carbonate solution (1.5 ml) is added. Upon standing the product precipitates. The dark red crystals are filtered, washed with water, and recrystallised from acetone; yield: ~65%; m.p. 178–180 °C (dec.).

The Zincke aldehyde 87 was prepared in 1904 by an independent method\[35\] using cyanogen bromide, pyridine, and N-methylaniline.

Zincke and Würker\[36\] were the first to realise that the pyridine ring was opened, when they prepared the polymethine salt 96 (X = Cl = 6) from pyridine.

These old preparations have been reinvestigated and an improved method has been published for the alkaline hydrolysis of the dianil\[39,97\]. The most convenient method for preparation of the Zincke aldehyde 87 is the König ring-opening with cyanogen bromide via the polymethine salt 96.

5-N-Methylanilinopenta-2,4-diyldiene-1-N-methylanilinium Bromide (96)\[39\]:
N-Methylaniline (15 g, 0.14 mol) and pyridine (5.6 g, 0.07 mol) are dissolved in ether (50 ml) and treated with a solution of cyanogen bromide (4.7 g, 0.07 mol) in ether (20 ml). The product 96 separates as blue crystals and can be recrystallised from water to give red needles; yield: 24 g (95%); m.p. 139 °C.

N-Methyl-N-phenyl-5-amino-trans-2,trans-4-pentadienal (87; Zincke Aldehyde)\[98\]:
A solution of the salt (96, 20 g, 0.056 mol) in methanol (100 ml) is added to a mixture of sodium hydroxide (2.6 g, 0.065 mol), water (15 ml), and methanol (35 ml) at 35 °C. After addition, enough water is added to give a clear reaction mixture. After standing at 30 °C for 1 h, saturated sodium chloride solution (500 ml) is added and the reaction mixture is extracted with a benzene/ether mixture (1:1; 200 ml). The organic phase is washed with sodium chloride solution and dried with sodium sulfate, after which petroleum ether (~500 ml) is slowly added until the aldehyde separates. After crystallisation begins, additional petroleum ether (500 ml) is added, and the mixture is cooled for some hours at ~20 °C. The pale yellow needles of 87 are filtered; yield: 9.2 g (87%); m.p. 78–80 °C.

The corresponding 5-(N,N-diethylamino)-trans-2,trans-4-pentadienal\[99\] (97) can easily be prepared in fair yield (51%).

5-(N,N-Diethylamino)-trans-2,trans-4-pentadienal (97)\[99\]:
N-(2,4-Dinitrophenyl)-pyridinium chloride (94; 140.8 g, 0.5 mol) in ethanol (300 ml) is refluxed for 1 h with diethylenine (73.1 g, 1 mol), whereupon the cooled red reaction mixture is poured into water (600 ml). The separated 2,4-dinitroaniline is filtered and 5 molar sodium hydroxide solution (120 ml) is added. This mixture is left for 1 h, filtered, concentrated in vacuo and extracted with chloroform. The chloroform phase is washed with water and dried with sodium sulfate. Concentration in vacuo leaves a red oil. Distillation affords an orange red semi-crystalline oil; yield: 39 g (51%); b.p. 90–100 °C/0.001 torr; 170–171 °C/8 torr.

A variation of this method for the preparation of 5-piperidino-trans-2,trans-4-pentadienal (100) has been given\[96\].

This method has been used for the preparation of many N-mono-substituted 5-amino-2,4-pentadienals.

As an alternative practical example, the preparation of 5-(N,N-dimethylanilino)-2,4-pentadienal (101), reported by Malhotra and Whiting\[91\] is also given.
Synthesis and Reactions of Glutaconaldehyde and 5-Amino-2,4-pentadienals

5-(N,N-Dimethylamino)-trans,trans-4-pentadienal (101): 1-(2,4-Dinitrophenyl)-pyridinium chloride (94; 100 g, 0.36 mol) in ethanol (1 l) is treated with 25% aqueous dimethylamine (120 ml). The mixture is heated at 60–70 °C for 30 min, evaporated under reduced pressure, and treated with cold water (600 ml). The separated 2,4-dinitroaniline is collected and the filtrate is made alkaline with sodium hydroxide (20 g) in water (100 ml) and extracted with dichloromethane (4 × 150 ml). Evaporation of the dried extract leaves a hydroscopic solid, which from analytical data appears to be an unstable hydrate; yield: 34 g (76%); m.p. 30–32 °C. After distillation (118–125 °C/0.15 torr; m.p. 59 °C), it is reconverted into the hydrate, which crystallises upon standing; m.p. 30 °C.

The crystalline 5-morpholino-trans,trans-4-pentadienal (m.p. 120–123 °C) may be prepared by the same method.

Pyrylium salts 103 or 4-methyl-N-(2,4-dinitrophenyl)-pyridinium chloride (104) may be used as a source of the 5-aminopentadienals 107.

These compounds 107 are isoprene derivates and as such give access to syntheses in the vitamin A-series. The isoprene unit 109 can also be obtained from reaction of alkyne 108 with dimethylamine; this method also gives fair yield from simple starting materials.

Finally, the Vilsmeier reaction can be used for the preparation of 5-amino-2,4-pentadienals.
The bis-iminium salt 115 prepared in fair yield from a dibromide and pyridine also reacts to give the unstable aldehyde 114 (R = H).

Most of the known 5-amino-2,4-pentadienes have been prepared by one of the above described methods. Table 4 gives the data and references for these compounds, and contains mainly the preparatively useful examples.

### Table 4. Selected 5-Amino-2,4-pentadienes

<table>
<thead>
<tr>
<th>Compound</th>
<th>Starting material</th>
<th>Yield [%]</th>
<th>m.p. [°C] or b.p. [°C]/torr</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>H₂N=CH-N=N-H</td>
<td><img src="image" alt="N=N=CH-N=N-H" /></td>
<td>100</td>
<td>b</td>
<td>106</td>
</tr>
<tr>
<td>UO₂(NO₃)₂ • H₂N=CH-N=N-H</td>
<td><img src="image" alt="UO₂(NO₃)₂ • H₂N=CH-N=N-H" /></td>
<td>–</td>
<td>–</td>
<td>107</td>
</tr>
<tr>
<td>6-CH₃-N=CH-N=N-H</td>
<td><img src="image" alt="6-CH₃-N=CH-N=N-H" /></td>
<td>74</td>
<td>168–171°</td>
<td>108, 109</td>
</tr>
<tr>
<td>H₂C-6-CH₃-N=CH-N=N-H</td>
<td><img src="image" alt="H₂C-6-CH₃-N=CH-N=N-H" /></td>
<td>76</td>
<td>178°</td>
<td>109, 110</td>
</tr>
<tr>
<td>N=N=CH-N=N-H</td>
<td><img src="image" alt="N=N=CH-N=N-H" /></td>
<td>45</td>
<td>185°</td>
<td>110</td>
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<tr>
<td>H₂CO-6-CH₃-N=CH-N=N-H</td>
<td><img src="image" alt="H₂CO-6-CH₃-N=CH-N=N-H" /></td>
<td>66</td>
<td>166°</td>
<td>109, 110</td>
</tr>
<tr>
<td>H₂C-6-CH₃-N=CH-N=N-H</td>
<td><img src="image" alt="H₂C-6-CH₃-N=CH-N=N-H" /></td>
<td>–</td>
<td>240°</td>
<td>111</td>
</tr>
<tr>
<td>O₂N-6-CH₃-N=CH-N=N-H</td>
<td><img src="image" alt="O₂N-6-CH₃-N=CH-N=N-H" /></td>
<td>90</td>
<td>180°, 175° (acetone)</td>
<td>83, 92, 93, 109</td>
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<tr>
<td>O₂N-6-CH₃-N=CH-N=N-H</td>
<td><img src="image" alt="O₂N-6-CH₃-N=CH-N=N-H" /></td>
<td>92</td>
<td>161°</td>
<td>72, 93, 112, 113</td>
</tr>
<tr>
<td>O₂N-6-CH₃-N=CH-N=N-H</td>
<td><img src="image" alt="O₂N-6-CH₃-N=CH-N=N-H" /></td>
<td>69</td>
<td>135–136°</td>
<td>93, 113</td>
</tr>
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</table>
Table 4. (Continued)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Starting material</th>
<th>Yield [%]</th>
<th>m.p. [°C] or b.p. [°C]/torr</th>
<th>Reference</th>
</tr>
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<tr>
<td><img src="image1" alt="Chemical Structure" /></td>
<td><img src="image2" alt="Chemical Structure" /></td>
<td>90</td>
<td>154° (dec) (C2H5OH)</td>
<td>114</td>
</tr>
<tr>
<td><img src="image3" alt="Chemical Structure" /></td>
<td><img src="image4" alt="Chemical Structure" /></td>
<td>90</td>
<td>270° (dec)</td>
<td>115</td>
</tr>
<tr>
<td><img src="image5" alt="Chemical Structure" /></td>
<td><img src="image6" alt="Chemical Structure" /></td>
<td>65</td>
<td>207°</td>
<td>109</td>
</tr>
<tr>
<td><img src="image7" alt="Chemical Structure" /></td>
<td><img src="image8" alt="Chemical Structure" /></td>
<td>74</td>
<td>61°</td>
<td>116, 117</td>
</tr>
<tr>
<td><img src="image9" alt="Chemical Structure" /></td>
<td><img src="image10" alt="Chemical Structure" /></td>
<td>76</td>
<td>69° (c-C6H12)</td>
<td>66</td>
</tr>
<tr>
<td><img src="image11" alt="Chemical Structure" /></td>
<td><img src="image12" alt="Chemical Structure" /></td>
<td>72</td>
<td>171°</td>
<td>66</td>
</tr>
<tr>
<td><img src="image13" alt="Chemical Structure" /></td>
<td><img src="image14" alt="Chemical Structure" /></td>
<td>63</td>
<td>98°</td>
<td>66</td>
</tr>
<tr>
<td><img src="image15" alt="Chemical Structure" /></td>
<td><img src="image16" alt="Chemical Structure" /></td>
<td>68</td>
<td>126–126.5° (H2O)</td>
<td>118</td>
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<tr>
<td><img src="image17" alt="Chemical Structure" /></td>
<td><img src="image18" alt="Chemical Structure" /></td>
<td>42</td>
<td>122–123° (C6H6/C6H5OH)</td>
<td>118</td>
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<tr>
<td><img src="image19" alt="Chemical Structure" /></td>
<td><img src="image20" alt="Chemical Structure" /></td>
<td>30–35</td>
<td>195–196°</td>
<td>118</td>
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<tr>
<td><img src="image21" alt="Chemical Structure" /></td>
<td><img src="image22" alt="Chemical Structure" /></td>
<td>–</td>
<td>112–113° (dec) (C2H3OH/H2O)</td>
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<td><img src="image23" alt="Chemical Structure" /></td>
<td><img src="image24" alt="Chemical Structure" /></td>
<td>–</td>
<td>d</td>
<td>119</td>
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<tr>
<td><img src="image25" alt="Chemical Structure" /></td>
<td><img src="image26" alt="Chemical Structure" /></td>
<td>77</td>
<td>30–32° (118–125°/0.15)</td>
<td>11, 20, 102</td>
</tr>
<tr>
<td><img src="image27" alt="Chemical Structure" /></td>
<td><img src="image28" alt="Chemical Structure" /></td>
<td>85</td>
<td>45–48° (116–119°/0.1)</td>
<td>120</td>
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<td><img src="image29" alt="Chemical Structure" /></td>
<td><img src="image30" alt="Chemical Structure" /></td>
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<td>69° (120°/1.1)</td>
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<tr>
<td><img src="image31" alt="Chemical Structure" /></td>
<td><img src="image32" alt="Chemical Structure" /></td>
<td>48</td>
<td>64° (129°/0.1)</td>
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<td><img src="image33" alt="Chemical Structure" /></td>
<td><img src="image34" alt="Chemical Structure" /></td>
<td>50</td>
<td>69° (124°/0.5)</td>
<td>102</td>
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</tbody>
</table>
Table 4. (Continued)

<table>
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<tr>
<th>Compound</th>
<th>Starting material</th>
<th>Yield [%]</th>
<th>m.p. [°C] or b.p. [°C]/torr</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>C₂H₅N=N=CH₂</td>
<td></td>
<td>51, 28</td>
<td>170–171°/8</td>
<td>98, 121</td>
</tr>
<tr>
<td>C₂H₅N=N=CH₂</td>
<td></td>
<td>23</td>
<td>57.5–58° (110–111°/0.05)</td>
<td>101</td>
</tr>
<tr>
<td>H₃C=N=C=CHO</td>
<td></td>
<td>50</td>
<td>orange oil</td>
<td>40</td>
</tr>
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<td></td>
<td></td>
<td>45</td>
<td>79–80° (toluene)</td>
<td>76</td>
</tr>
<tr>
<td></td>
<td></td>
<td>51</td>
<td>120–123°</td>
<td>99</td>
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<tr>
<td></td>
<td></td>
<td>87</td>
<td>78°</td>
<td>40, 89, 103</td>
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<td></td>
<td></td>
<td>100</td>
<td>115–116° (C₂H₅O)</td>
<td>54</td>
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<td></td>
<td></td>
<td>34</td>
<td>85°</td>
<td>40, 72</td>
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<tr>
<td></td>
<td></td>
<td>56</td>
<td>126–127°</td>
<td>40, 72</td>
</tr>
<tr>
<td></td>
<td></td>
<td>36</td>
<td>114–115°</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td></td>
<td>43</td>
<td>84°</td>
<td>40</td>
</tr>
<tr>
<td>H₃C=N=CH₂</td>
<td></td>
<td>35</td>
<td>159–161° (subl.) (C₂H₅O)</td>
<td>20</td>
</tr>
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</table>

a Further examples may be found in the references cited.

b Characterised by U.V. spectrum.

c Characterised by I.R. and U.V. spectra and microanalysis.

d Unstable yellow powder recrystallised from acetic acid.

6.3. Reactions with Active Methylene Compounds

The reactive aldehyde functionality in glutaconaldehyde and its derivatives reacts with active methylene groups. This reaction has been utilised analytically for the detection of compounds containing active methylene groups and only in some cases have these reaction products been characterised. The Wittig reactions of glutaconaldehyde enol esters were discussed in Section 4.1.3.

Most of these syntheses are not performed with the glutaconaldehyde as such, but rather with pyridini-

um compounds or the glutaconaldehyde anils, as well as with the Zincke aldehydes obtained from pyridine. Many of the products from these extensively studied reactions are not well characterised and are mainly mentioned in patents concerning polymethine dyes. The early examples of the known reaction products of these types have been reviewed. Reactions of the Zincke aldehydes with active methylene compounds such as 117 have been reviewed.
Some products of the polymethine type from the ring opening reactions of pyridinium compounds with active methylene compounds have been characterised\textsuperscript{124}, for example zoln red 119 obtained from pyridine and a pyrazole, on ring opening with sodium cyanide. A similar product 120 from the reaction of pyridine, an acid chloride, and 2-oxobenzofuran has been reported\textsuperscript{125}.

A related product, 125, obtained from the reaction of dichlorodiphenylmethane, pyridine, acetone, and sodium hydroxide was recently identified\textsuperscript{127}. The structure of this product was confirmed by an X-ray investigation, and is an example of a stable pyridine ring-opened product with cis-conformation.

It was also shown\textsuperscript{125} that a Zincke aldehyde could be condensed with an active methylene compound, such as 2-oxobenzofuran to give 121. Also phenylmethylpyrazolone and dimedone reacted to give similar products.

The aldehyde obtained by simple ring opening from bis-pyridinium salts such as 115 has been assigned\textsuperscript{117} the all-trans structure 122 from N.M.R. spectral analysis.

When such ring opening reactions are performed in acetone, further reaction may take place\textsuperscript{126} to give products such as 124.
The N-methoxypyridinium perchlorates are easily obtained from the appropriate N-oxides by O-methylation. The results of these reactions are summarised in Table 5.

### Table 5. 1-Methoxylimino-trans-2,trans-4-pentadienes 133

<table>
<thead>
<tr>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>R⁴</th>
<th>Yield [%]</th>
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<tbody>
<tr>
<td>H</td>
<td>CN</td>
<td>H</td>
<td>H</td>
<td>H₂C- COO</td>
</tr>
<tr>
<td>H</td>
<td>CN</td>
<td>H</td>
<td>H</td>
<td>C₆H₅- COO</td>
</tr>
<tr>
<td>H</td>
<td>H</td>
<td>H</td>
<td>CO-NH₂</td>
<td>(H₃C)₂N</td>
</tr>
<tr>
<td>H</td>
<td>H</td>
<td>H</td>
<td>CO</td>
<td>1-pyrolidinyl</td>
</tr>
<tr>
<td>H</td>
<td>H</td>
<td>H</td>
<td>CO</td>
<td>1-piperidinyl</td>
</tr>
<tr>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H₂C- COO</td>
<td>62</td>
</tr>
<tr>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H₂C- COO</td>
<td>34</td>
</tr>
<tr>
<td>H</td>
<td>H</td>
<td>H</td>
<td>(H₃C)₂N</td>
<td>28</td>
</tr>
<tr>
<td>H</td>
<td>H</td>
<td>H</td>
<td>1-piperidinyl</td>
<td>82</td>
</tr>
<tr>
<td>H</td>
<td>H</td>
<td>H</td>
<td>1-pyrolidinyl</td>
<td>89</td>
</tr>
</tbody>
</table>

The syntheses of pentadienes (yield varying from 21–60%) by the ring opening of N-methoxypyridinium perchlorates with active methylene compounds and base was also demonstrated, as shown by the preparation of 134.

### Polycenes from N-Methoxypyridinium Perchlorates and Active Methylene Compounds

#### General Procedure:
The pyridinium perchlorate (1 mmol) and the active methylene compound (1 mmol) are dissolved in cold dimethylformamide or hexamethylphosphoramide triamide (2 ml), whereupon triethylamine (4–5 drops) is added. Neutralisation at 0 °C with 3 molar aqueous hydrochloric acid and addition of cold water (6–8 ml) precipitates the polycenes. They are purified by dissolving the crystals in acetone/dimethylformamide (1:1), addition of activated carbon, followed by filtration, and reprecipitation with cold water.

These syntheses have all been performed with electronegatively substituted pyridines, for example 2-, 3-, and 4-cyanopyridines, alkylpyridines did not react. Some alkyl-substituted glutacaldehyde derivatives were also prepared by another procedure. These derivatives were less stable.
Ring opening of the N-methoxypyrindinium salt 135 with ammonia at \(-50\,^\circ\text{C}\) was reported\textsuperscript{129} to give the unstable product 136, to which the cis-trans stereochemistry has been assigned. The stereochemistry was suggested on the basis of the \(^1\text{H}-\text{N.M.R. spectrum.}\)

\[
\begin{array}{c}
\text{135} \\
\text{136}
\end{array}
\]

Also, substituted pyridines such as, 137, 138, 139, showed the expected ring-open products. The stereochemistry of these ring openings is in accordance with previous results\textsuperscript{130}. Here the ring openings of pyridine N-oxides with Grignard reagents resulted in the formation of the cis-isomers 140.

The stereochemistry was confirmed here by rearrangement to the more stable all-trans isomers.

\[
\begin{array}{c}
\text{137} \\
\text{138} \\
\text{139} \\
\text{140}
\end{array}
\]

From the examples discussed above it can be concluded that these reactions of pyridinium derivatives often give rise to polyenes difficult to obtain by other routes. This can be illustrated by the preparation\textsuperscript{131} of the polyene 142.

\[
\begin{array}{c}
\text{141} \\
\text{142} \quad R = \text{H, COCH}_2, \text{COOC}_2\text{H}_5 \quad \text{X}^1 = \text{CN} \quad \text{X}^2 = \text{CN, COOCH}_2, \text{SO}_2\text{C}_6\text{H}_5, \text{CN, COOC}_6\text{H}_5, \text{CONH}_2
\end{array}
\]

Quite recently\textsuperscript{132} the ring opening of some N-alkoxy-pyridinium salts have been reported, and it was definitely demonstrated that the primary ring opened product had a cis structure.

\[
\begin{array}{c}
\text{143} \\
\text{144} \\
\text{145}
\end{array}
\]

This product 143 indicated\textsuperscript{133} the following mechanism for the disrotatory, thermally allowed ring opening of the dihydropyridine ring 144, and confirms the statement given in the beginning of Section 6.1, namely that the cis-conformation of the pyridine 5,6-double bond is preserved in the primary ring opened products such as in compound 145 when the nucleophile reacts at the 2-position of pyridine.

\[
\text{Received: March 12, 1979} \\
\text{(Shortened version: October 16, 1979)}
\]

\begin{footnotesize}
\textsuperscript{2} J. Becher, \textit{Acta Chem. Scand.} 26, 3627 (1972).
\end{footnotesize}
35 A detailed method for the preparation of the pyridine from the gluconolactone anhydride is given in Ref.36.
47 J. Becher, unpublished results.
59 (a) F. W. Bergstrom, Chem. Rev. 35, 103 (1944).
Synthesis and Reactions of Glutaconaldehyde and 5-Amino-2,4-pentadienals

A. C. Bruce, W. Müller, Justus Liebigs Ann. Chem. 333, 296 (1904).

(b) T. Zinke, Justus Liebigs Ann. Chem. 341, 365 (1905); 330, 361 (1903).

(c) Y. Tamura, K. Semoto, M. Mano, T. Masui, Yakugaku Zasshi 92, 371 (1972); C. A. 77, 34126 (1972); see also Ref. 96.


(g) König, J. Prakt. Chem. 69, 105 (1904).

(h) Zinke, T. Würker, Justus Liebigs Ann. Chem. 338, 121 (1904); 338, 127 (1904).

(i) Also Ref. 11 for a procedure.


(k) J. Becher, unpublished results.


(x) Y. Tamura, N. Tsunimoto, M. Uchimura, Yakugaku Zasshi 91, 72 (1971); C. A. 74, 9804 (1971); see also Ref. 17.


(z) E. P. Lira, J. Heterocycl. Chem. 9, 713 (1972).


(b) F. Kröhnke, H. Leister, Chem. Ber. 91, 1295 (1958); cf. also Ref. 18.

(c) G. W. Fischer, Chem. Ber. 103, 3489 (1970); Z. Chem. 8, 389 (1968).


(h) F. Kröhnke, Angew. Chem. 75, 181 (1963), and refs. cited therein.


G. M. Coppola, *Synthesis* 1980 (7), 505–536; The structures of compounds 43 (p. 511), 122 (p. 520), and 241 (p. 533) should be as shown below:

![Chemical Structures](image)

J. Diago-Meseguer, A. L. Palomo-Coll, J. R. Fernández-Lizarbe, A. Zugaza-Bilbao, *Synthesis* 1980 (7), 547–551; The substituent R in Table 1 entries 2 and 20 and Table 2, entry 1 should be:

\[
N^2 - CH_2^+\]

A more correct name for reagent 4 (as used in index) is 3,3'-{(Chlorophosphorylidene)-bis[2-oxo-1,3-oxazolidine]}.

J. Becher, *Synthesis* 1980 (8), 589–612; The structure of compound 36 (p. 593) should be:

![Chemical Structure](image)

H. Paulsen, F. R. Heiker, J. Feldmann, K. Heyns, *Synthesis* 1980 (8), 636–638; The correct name for reagent 1 is 3-methyl-2-selenoxo-2,3-dihydro-

1,3-benzothiazole.

G. Sosnovsky, J. A. Krogh, *Synthesis* 1980 (8), 654–656; The first line of the text should read: In 1978, Olah and Vankar reported1 the conversion of

D. A. Walsh, *Synthesis* 1980 (9), 677–688; The correct name for compound 39 (p. 680) is N'-{(2-Carboxyphenyl)-N,V-dimethylformamidinidene}.

M. A. Smoczkiwicz, J. Jasieczak, *Synthesis* 1980 (9), 739–740; Compounds 2 should be named as 20,21-dideo derivatives; the name for compound 1a (p. 740) Table 1 should be 21-hydroxy-3,20-dioxopregna-4-ene.


Abstract 5885, *Synthesis* 1980 (9), 761; The title should be: Alkylation of 5-Methyl-3-Oxoalkanethioate.

T. Wagner-Jauregg, *Synthesis* 1980 (10), 769–798; The name of compounds 52a and b (p. 772) should be cis- and trans-1-methyl-3-phenylindan.

The heading for Table 2 (p. 784) should be:

**Tabelle 2. Herstellung von 1-Arylacacenaphthen-Derivaten durch Photocyclisierung von 1-(1-Arylethenyl)-napthalindervaten in Abwesenheit von Oxidationsmitteln**

The structures of the products in this Table should be of the type:

![Chemical Structures](image)

The first paragraph on p. 785 (right-hand side) should read: Aus den konjugierten 1,2-Diiminen 667 und Phenyl-isocyanaten oder Benzoyl-isocyanat entstehen criss-cross-Addukte (668, Schema 2.2.1-E)441,442.

The last line on p. 794 should read:

und der Hydroxaminsäuren353 deutlich gesteigert533.

Reference 441 (p. 796) should be:


H. Alper, D. E. Laycock, *Synthesis* 1980 (10), 799; The last structure for R' – R2 in the Table should be:

![Chemical Structure](image)

T. Takajo, S. Kambe, *Synthesis* 1980 (10), 833–836; Products designated as 4a,b,c,d in Table 1 (p. 834) and Table 2 (p. 835) should be designated as 4a, b, f, g, respectively.

P. Di Cesare, P. Duchaussay, B. Gross, *Synthesis* 1980 (11), 953–954; The first formula scheme (p. 954) should be:

![Chemical Structure](image)

Z. H. Kudzin, W. J. Stec, *Synthesis* 1980 (12), 1032–1034; The heading for the first procedure (p. 1033) should be: 3-(Tris-[(butoxy)iodylihthio])-propional [3 (R = (n-C6H13)O3S]l.

R. E. Zipkin, N. R. Natale, I. M. Taffer, R. O. Hutchins. *Synthesis* 1980 (12), 1035–1036; The substituents R' – R2 in the Table for product 4e should be:

\[-(CH_2)_3-\]

Abstract 5948, *Synthesis* 1980 (12), 1040; Compounds 2 should be named carboximidimid dichlorides.

Abstract 5963, *Synthesis* 1980 (12), 1045; The title should be: Acyl Fluorides, Chlorides, Bromides, and Iodides from Carboxylic Acids.