The Acyllactone Rearrangement; A Method for the Preparation of Heterocyclic Ring Systems (1, 2)

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Introduction

Cyclic derivatives of carboxylic acids, such as lactones, thiolactones, or lactams can be converted by partial reduction into heterocycles of the same ring size. Lactones thus form cyclohemiacetals or diols, which can be cyclized by the addition of acid. This process presents certain preparative difficulties however, and is not much investigated from the point of view of its general applicability. Furthermore, the unsubstituted heterocycles thus obtained offer few possibilities of building up a second ring system at a definite position. In the course of our investigations into the gentian bitter principle, gentiopierin, it became necessary to synthesize bicyclic hemiacetallactones (I) in order to confirm the proposed constitution (3). During the course of this work, we discovered a rearrangement reaction characteristic of α-acyllactones, in which di- and tetrahydrofuran or pyran derivatives are readily obtained by the proton-catalyzed alcoholysis of substituted γ- or δ-lactones. We designated this reaction the α-hydroxyalkyldenelactone rearrangement.

Lactones with other α-acyl esters, e.g., α-hydroxymethylenearyl or α-oximino can also be converted. β-Acylactones are also capable of undergoing a rearrangement (see p. 218). We should therefore prefer to name the reaction more generally and briefly the acyllactone rearrangement. Further investigation showed that the reaction can also be effected in an aqueous medium; heterocyclic acids or their decarboxylation products are then produced. Inspection of the literature revealed that the rearrangement in $\text{H}_2\text{O}/\text{H}^+$ had successfully been applied to synthetic work on many previous occasions. All the reactions can be included under the common heading of acyllactone rearrangement and, depending on the constitution of the acyl compound and on the rearrangement medium, they can be classified according to definite reaction sequences. In this review, we hope to give a survey of the work to date and the results
obtained, and to show the limitations in the application of the acylactone rearrangement.

Preparative Methods

Preparation of the \( \alpha \)-Acyl Derivatives

The rearrangement proceeds according to the general scheme

\[
\begin{align*}
\text{X} = & \quad \text{O, S, N} \\
\text{R} & \quad \text{H, CeO}, \text{NaOC} \\
\text{R'} & \quad \text{H, CeO} \\
\text{CO}_2 & \quad \text{H} \\
\text{II} & \quad \text{Ha} \\
\text{III} & \quad \text{Ilia}
\end{align*}
\]

and is to be regarded as a sequence of equilibrium reactions \((4, 5)\). The \( \alpha \)-acylactones, -lactams and -thiolactones required as starting materials can be prepared in the following ways.

**By Ester Condensation**

Lactones or thiolactones, being internal esters, can be condensed with esters in the presence of an equimolar quantity of a base. The mixed ester condensation thus constitutes a general practical method for the preparation of \( \alpha \)-acylactones, in which the \( \alpha \)-acyl group can be varied within wide limits. Since many lactones are sensitive to bases and are converted into their open-chain isomers, the success of the reaction frequently depends on the condensing base employed. The following are among the condensing agents which can be used: powdered sodium or potassium, sodium ethoxide, sodium hydride, sodium amide, diisopropylaminomagnesium bromide, triphenylmethysiodium, sodium methyl-anilide, etc. \((4, 6-12)\).

Stable mono- and bicyclic \( \gamma \)- and \( \delta \)-lactones condense with oxalic or formic ester, and give yields of up to 80% when powdered sodium is used as the condensing agent \((13)\). Condensations with ethyl acetate give better yields with sodium hydride \((9)\), as the autocondensation of ethyl acetate in the presence of sodium to give acetoacetic ester reduces the yield of \( \alpha \)-acetyllactone.

\( \gamma \)-Carbethoxy-\( \delta \)-lactones (II) isomerize to \( \alpha \)-ethylideneglutaric acid half-esters (IIa) in the presence of sodium ethoxide; dihydrocoumarin (III) yields \( \alpha \),\( \beta \)-dihydrocoumaric ester (IIIa).
The condensation of these lactones with ethyl formate or ethyl oxalate can nevertheless be accomplished by the use of Grignard bases such as diisopropylaminomagnesium bromide \((10, 15)\).

\(\beta,\gamma\)- or \(\alpha,\beta\)-Unsaturated \(\delta\)-hydroxypentenoic acid lactones, e.g., IV, do not condense with esters, but isomerize under the influence of basic condensing agents to give substituted sorbic acids \((10)\).

![Chemical structure](image)

The unstable thiolactones are also best condensed by means of Grignard bases \((14–16)\). Ruzicka \((17)\) and Späth \((18)\) have reported on the condensation of lactams and both quinolinecarboxylic ester and nicotinic ester by the use of sodium ethoxide. Table 1 shows the yields of \(\alpha\)-ethoxalyl-\(N\)-methylpyrrolidone obtained under constant working conditions, and their dependence on the condensing base utilized \((11, 12)\).

The preparation of \(\alpha\)-acetyllactams by ester condensation has thus far been unsuccessful. The activation of the \(\alpha\)-position is weaker in the case of lactams than it is in that of lactones, with the result that the condensation does not proceed as readily. The \(\alpha\)-acylcarboxylic acid derivatives exhibit a higher ring stability compared to the unsubstituted parent substances, i.e., the lactones, thiolactones, and lactams \((15)\).

### Table 1

<table>
<thead>
<tr>
<th>Condensing agent</th>
<th>Yield of (\alpha)-Ethoxalyl-(N)-methylpyrrolidone (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diisopropylamino-Mg-Br</td>
<td>0</td>
</tr>
<tr>
<td>Sodium ethoxide</td>
<td>5.7</td>
</tr>
<tr>
<td>(\text{NaNH}_2)</td>
<td>6.1</td>
</tr>
<tr>
<td>Powdered sodium</td>
<td>4.8</td>
</tr>
<tr>
<td>((\text{C}_6\text{H}<em>8)</em>\text{Na})</td>
<td>11.1</td>
</tr>
<tr>
<td>((\text{C}_6\text{H}_8\text{NHCH}<em>3)</em>\text{Na})</td>
<td>21.1</td>
</tr>
<tr>
<td>Potassium</td>
<td>45.6</td>
</tr>
<tr>
<td>(\text{NaH})</td>
<td>70.0</td>
</tr>
</tbody>
</table>
By Direct Synthesis

Ring closure is especially effective for the one-step preparation of $\alpha$-acetyllactones. Thus, according to Lacey (19), various substituted $\alpha$-acetyl-$\gamma$- and -$\delta$-lactones are obtained from $\alpha$- or $\beta$-hydroxyaldehydes or -ketones with diketene, e.g., $\alpha$-acetylcoumarin (VI) from salicylaldehyde and diketene.

$\begin{align*}
\text{VI} & \quad \text{VII} \\
\end{align*}$

$\alpha$-Acetyllactones are similarly formed by the reaction between substituted propargyl alcohols and diketene (19). Dehydroacetic acid (VII) is obtained by the condensation of acetoacetic ester (20) or diketene (21). According to Knunjanz (22), $\alpha$-acetyl-$\gamma$-lactones (VIII) can be prepared from ethylene, propylene, or butylene (23) oxides and acetoacetic ester. $\alpha$-Acyllactones containing nitrogen in the ring are also formed by a simple ring closure. 4-Hydroxyalkylideneoxazolin-5-one (IX) can be prepared from sodium hippurate and acetic anhydride (24) or orthoformic ester (25) in this manner.

$\begin{align*}
\text{VIII} & \quad \text{IX} \\
\end{align*}$

Methods of Rearrangement

In Alcohol/H$^+$

Lactones which are readily opened by alcoholysis, e.g. mono- and bicyclic $\alpha$-acyl-$\delta$-lactones, rearrange even at room temperature. In order to effect the reaction, the $\alpha$-acyllactone is dissolved in 5-10 times its quantity of absolute alcohol to which 3-6% of hydrochloric or other acid has been added, and the solution allowed to stand for one or two days. The acid is then neutralized with saturated potassium carbonate or bicarbonate solution and the rearrangement product extracted with
ether. Yields of 80–95% are obtained throughout. More stable acyllactones, e.g. α-acetyl-γ-lactones, are rearranged in boiling alcohol/H⁺.

As shown in examples X, XI, and XII, heterocyclic carboxylic esters (XI) in equilibrium with the dihydrofuran or pyran form, XII, can thus be prepared from α-acyllactones. The R group in the α-acyl grouping appears in the rearrangement product XI at position 2, while the R' group contained in the rearrangement solvent becomes linked to position 2 via the oxygen atom and to position 3 in the ester grouping. Distillation of the rearrangement product XI in the presence of catalytic amounts of polyphosphoric or sulfuric acid yields the pure dihydro compound XII via R'OH elimination. The preparation of the pure tetrahydrofuran or pyran compound XI is best achieved by effecting the rearrangement in higher alcohols, since the mixtures of dihydro and tetrahydro forms obtained are then more readily separated by distillation (see Experimental section). The rearrangement, consisting of a sequence of equilibrium reactions, is reversible. If the ester XII is dissolved in 30% perchloric acid and 2,4-dinitrophenylhydrazine added, the 2,4-dinitrophenylhydrazone of the α-acyl compound X is obtained. The composition of the mixture of XI and XII resulting from the rearrangement is affected by both the ring size and the substitution. In the case of the six-membered α-hydroxymethylene- and α-ethoxallyllactones the proportion of dihydro product XII lies between 10 and 20%, while with the corresponding five-membered lactones it is 1–5%. If, as in the rearrangement of the α-acetyl-γ- and δ-lactones, the product contains a methyl group in position 2, the proportion of dihydro product rises appreciably and lies between 40 and 60%. In the pyrancarboxylic esters XIa, an additional methyl group in the Cα-position causes a further displacement in the equilibrium, to 90% of XIIa. This phenomenon can be accounted for by the steric hindrance resulting from the reciprocal effect of the two axial 2,6-methyl groups. The unsaturated dihydropyran XIIa, which exists in the strainless half-chair conformation XIIb, is formed by the elimination of methanol (9).

IN AQUEOUS ACID

If the rearrangement is carried out in concentrated hydrochloric acid, the acyl compound is dissolved in the acid—which contains added
acetic acid or dioxane in the case of more insoluble compounds—and the solution allowed to stand at room temperature or in the refrigerator (0°). In rearrangements involving decarboxylation the equilibrium is shifted in favor of the rearrangement product by the crystallization of the heterocyclic carboxylic acid or the evolution of CO₂. The isolation of soluble rearrangement products is accomplished by neutralizing the solution with alkali carbonate and extracting with ether.

Rearrangement of stable acyllactones in dilute acids (e.g., 2N HCl, 2N H₂SO₄, 2N HClO₄) is effected by heating under reflux, when decarboxylation usually occurs. This can be avoided in some cases by working at room temperature or by cooling in ice.

Special Methods

The rearrangement of α,β-unsaturated α-acyl-γ-lactones to furan-3-carboxylic acids is carried out in acetic acid/HCl or acetic acid/H₂SO₄ (19). The double bond migrates to the β,γ-position during the reaction. BF₃ etherate or AlCl₃ can also be used (19).

In the rearrangement of acyl-γ-lactams by hydrolysis with concentrated HCl, the ring closure to the pyrrolidine presents some difficulty. It can be accomplished by the hydrogenation of the carbonyl of the acyl group followed by iodination of the hydroxyl group and elimination of HI (see pp. 211–213).

α-Acyloxazolin-5-ones can be opened by alcohysis, and only ring-close to the oxazole-4-carboxylic ester after heating with SOCl₂ or a mixture of H₂SO₄ and acetic anhydride (26).

The method of Cornforth represents a special variant of the rearrangement process; according to this modification, the sodium salts of oxazole-4-carboxylic acids are obtained by heating the sodium salts of the hydroxyalkylideneoxazolin-5-ones (see p. 213). The rearrangement of some nitrogen heterocycles is favored by the presence of strong alkali hydroxides (27–29) (see p. 214).

Special Reactions

Rearrangement of α-Acyl-δ-lactones

The preparation of alkyl-substituted α-acyl-δ-lactones presents no difficulty. The ester condensations with formic, oxalic, and acetic ester proceed in good yield when powdered sodium or sodium hydride is used as the condensing agent. Table 2 shows a number of rearrangement products (XIVa to XIVI) and the yields obtained. The corresponding dihydropyran compounds XVa to XVI are readily obtained by distillation with polyphosphoric acid.
γ-Carbothoxy-8-caprolactones isomerize to α-ethylidene glutaric esters when the condensation with powdered sodium or sodium ethoxide is attempted (10). The ester condensation can nevertheless be accomplished by the use of strongly basic condensing agents such as sodium amide, sodium hydride, and especially diisopropylaminomagnesium bromide (10, 33). The rearrangement of the α-acyl-γ-carboethoxylactones in ethanol/H⁺ gives good yields of dihydropyran-3,5-di- and 2,3,5-tricarboxylic esters (Table 3).

The formation of stable cyclohemiacetals of type XIX during the rearrangement of primary and secondary α-ethoxalyl-8-lactones is not without interest. The structural evidence was adduced by degradation
TABLE 3
Products of the Rearrangement of α-Acyl-γ-carbethoxy-δ-lactones

<table>
<thead>
<tr>
<th>XVI</th>
<th>XVII</th>
<th>XVIII</th>
</tr>
</thead>
<tbody>
<tr>
<td>R¹</td>
<td>R²</td>
<td>R³</td>
</tr>
<tr>
<td>a</td>
<td>CH₃</td>
<td>H</td>
</tr>
<tr>
<td>b</td>
<td>CH₃</td>
<td>H</td>
</tr>
<tr>
<td>c</td>
<td>CH₃</td>
<td>CH₃</td>
</tr>
</tbody>
</table>

*When not indicated otherwise R⁴ = R⁴.

A benzoylbutyrolactone (XXVI) rearranges in an analogous manner, yielding 2-phenyl-substituted tetrahydro or dihydrofuran derivatives (XXVIIa and b) (34).

An exceptional reaction course is followed during the rearrangement of compound XIX (9). Apart from the normal rearrangement product XXII, the decarboxylation products XX and XXI can also be isolated. The reaction can be explained by the formation of a methanetricarboxylic acid-type intermediate and the latter’s subsequent decarboxylation (9).

Rearrangement of α-Acyl-γ-lactones

Good yields of α-acetyl-γ-lactones are obtained via ester condensation by the use of powdered sodium. α-Acetyl-γ-lactones can also be prepared according to the method described by Knunjanz (22, 9, 23). The rearrangement in methanol or ethanol/H⁺ results in the formation of 2-alcohol tetrahydrofurans, which are readily converted into the corresponding dihydrofuran derivatives by the elimination of alcohol (Table 4).

α-Benzyolbutyrolactone (XXVI) rearranges in an analogous manner, yielding 2-phenyl-substituted tetrahydro or dihydrofuran derivatives (XXVIIa and b) (34).
THE ACYLLACTONE REARRANGEMENT

![Diagram of acyldiol rearrangement](image)

**TABLE 4**

<table>
<thead>
<tr>
<th>XXIII</th>
<th>XXIV</th>
<th>XXV</th>
<th>Lit. ref.</th>
<th>Yield (%)</th>
<th>B.p. (°C/mm Hg)</th>
<th>Yield (%)</th>
<th>B.p. (°C/mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R&lt;sup&gt;1&lt;/sup&gt;</td>
<td>R&lt;sup&gt;2&lt;/sup&gt;</td>
<td>R&lt;sup&gt;3&lt;/sup&gt;</td>
<td>R&lt;sup&gt;4&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>CH₃</td>
<td>82</td>
<td>85-86/13</td>
<td>79</td>
</tr>
<tr>
<td>b</td>
<td>H</td>
<td>H</td>
<td>CO₂C₃H₇</td>
<td>CH₃</td>
<td>54</td>
<td>72-75/0.03</td>
<td>88</td>
</tr>
<tr>
<td>c</td>
<td>H</td>
<td>H</td>
<td>CH₃</td>
<td>CH₃</td>
<td>40*</td>
<td>74-77/12</td>
<td>93</td>
</tr>
<tr>
<td>d</td>
<td>CH₃</td>
<td>H</td>
<td>H</td>
<td>CH₃</td>
<td>60</td>
<td>84/9</td>
<td>81</td>
</tr>
<tr>
<td>e</td>
<td>CH₃</td>
<td>H</td>
<td>CH₃</td>
<td>CH₃</td>
<td>71</td>
<td>66/0.01</td>
<td>-</td>
</tr>
<tr>
<td>f</td>
<td>CH₃</td>
<td>H</td>
<td>CH₃</td>
<td>CH₃</td>
<td>43*</td>
<td>75-78/11</td>
<td>92</td>
</tr>
<tr>
<td>g</td>
<td>CH₃</td>
<td>CH₃</td>
<td>H</td>
<td>CH₃</td>
<td>64</td>
<td>84-85/9</td>
<td>86</td>
</tr>
<tr>
<td>h</td>
<td>CH₃</td>
<td>CH₃</td>
<td>CO₂C₃H₇</td>
<td>C₅H₅</td>
<td>61</td>
<td>76-78/0.01</td>
<td>91</td>
</tr>
<tr>
<td>i</td>
<td>CH₃</td>
<td>CH₃</td>
<td>CH₃</td>
<td>CH₃</td>
<td>70*</td>
<td>36-41/0.2</td>
<td>90</td>
</tr>
</tbody>
</table>

* Mixed with XXVI.

α-Oximino-γ-butyrolactone (XXVIII), obtainable from α-aceto-γ-butyrolactone and ethyl nitrite (35), can be rearranged in methanol/H⁺ to give 2-hydroxy-3-carboxmethoxyisoxazolidine (XXIX) (34).

α-Hydroxymethylene-γ-butyrolactone couples with diazotized p-methoxyaniline at pH 7. Deformylation yields the azo compound or its tautomeric form, the p-methoxyphenylhydrazone XXX; the latter is re-
arranged and decarboxylated in boiling methanol containing traces of alkali, to give the pyrazoline derivative XXXI (27). An analogous rearrangement to the pyridazine system is known in the case of a δ-lactone hydrazone (35a).

\[
\begin{align*}
\text{XXX} & \xrightarrow{\text{CH}_2\text{OH, Traces of alkali}} \text{XXXI} \\
\end{align*}
\]

**Rearrangement of Bicyclic α-Acyl-γ- and -δ-lactones**

Bicyclic δ-lactones, which possess the same skeleton as the ant poison iridomyrmecin (36), can be condensed with esters in the presence of powdered sodium (8). The rearrangement in methanol or ethanol/H⁺ of the α-acyllactones (XXXII) which are formed results in good yields of hexahydroisochroman (XXXIII) or hexahydroisochromene derivatives (XXXIV) (8).

\[
\begin{align*}
\text{XXXIIa, b} & \xrightarrow{\text{R}^\text{I}OH/H^+} \text{XXXIIIa, b} & \text{XXXIVa, b} \\
\end{align*}
\]

Ester condensations of dihydrocoumarin and formic or oxalic ester can be effected by diisopropylaminomagnesium bromide; the use of sodium or sodium ethoxide results mainly in the formation of o-dihydrocoumaric ester. The rearrangement of the acyl compounds, XXXVa, b, yields derivatives of chroman (XXXVI) or chromene (XXXVII) (8).

\[
\begin{align*}
\text{XXXVa, b} & \xrightarrow{\text{R}^\text{I}OH/H^+} \text{XXXVIa, b} & \text{XXXVIIa, b} \\
\end{align*}
\]

Bicyclic α-acyl-γ-lactones (XXXVIII) are readily prepared via an ester condensation in the presence of sodium. Rearrangement in methanol or ethanol/H⁺ yields derivatives of hexahydrocoumaran (XXXIX) or hexahydrocoumarone (XL) (8).
Ester condensations with hemiacetallactones afford only small yields. The α-ethoxalylactone XLI rearranges to the diketal XLIa in ethanol/H⁺ (8).

Rearrangement of Macrocyclic α-Acyllactones

The acylation by ester condensation of macrocyclic lactones from ε-caprolactone upwards has thus far not been accomplished in satisfactory yield. The fundamental difficulty resides in the strong tendency shown by these lactones to polymerize in the presence of traces of soluble alkali. Thus ε-caprolactone could only be acylated to the extent of 1–2% by formic ester/sodium. Ester condensations using heptanolide (7-hydroxyheptanolactone) raised the yield to 10–15%; the major products are polymers such as di-, tetra-, or heptamer lactones (37). Grignard bases are completely useless as condensing agents. Alkyl-substituted lactones show in general a lower tendency to undergo polymerization. Thus, while say, δ-valerolactone cannot be subjected to ester condensation on account of the immediate onset of polymerization, α-acyl-δ-caprolactones are formed in good yield. Even β-methyl-ε-isopropyl-ε-caprolactone (mentholide) however, affords yields of only 2–5% of acyllactone by the ester condensation with sodium, potassium, or Grignard bases (38). Ring stabilization by alkyl substitution is no longer adequate in the case of ε-lactones. According to the investigations of Huisgen and Ott (39), a cis to trans change in configuration occurs in lactones of medium ring size. The trans-lactones, from approximately...
nonalide onwards, again display an increased stability; this is evidenced by the hydrolysis constants, for example, which are of the same order as the constants of open-chain trans-esters. Ester condensations should therefore proceed more favorably again from nonalide upwards. In condensation experiments with 15,1-hexadecanolide, however, no acyl product could be detected (40). Compared to the \( \gamma \)- and \( \delta \)-lactones, the macrocyclic trans-lactones manifestly occupy a special position in chemical reactions; also, they are hardly comparable to the homologous open-chain esters in their chemical behavior [cf. their behavior during Friedel-Crafts reaction (41)].

If the crude condensation products of mentholide containing 2–5\% of the acyl compound XLII are dissolved in methanol/H\( ^{+} \), the enol reaction with FeCl\( _{3} \) and the UV absorption band at 240 m\( \mu \) due to the acyl compound both disappear after a certain time. This can be explained by either a rearrangement to XLIII or the formation of the acetal XLIIIa. No well-defined products have thus far been isolated in pure form.

Rearrangement of \( \alpha \)-Acyl-\( \gamma \)- and -\( \delta \)-thiolactones

In the ester condensation of \( \gamma \)- and \( \delta \)-thiolactones, the best yields are obtained by the use of diisopropylaminomagnesium bromide or sodium hydride as condensing agent (8,14–16). In contrast to the oxygen homologs, no 2-alkoxytetrahydro compounds are formed during the rearrangement; instead, the elimination of alcohol results in the immediate formation of the 2-alkoxydihydro compounds. The elimination of alcohol is promoted by the pronounced participation of the free electron pairs of sulfur in the mesomeric system (cf. the section on optical measurements). \( \alpha \)-Acyl-\( \gamma \)-thiolactones (XLIV) and \( \alpha \)-acyl-\( \delta \)-thiolactones (XLVI) yield 4,5-dihydrothiophene-3-carboxylic esters or -2,3-dicarboxylic esters (XLV, Table 5) and 5,6-dihydrothiopyran-3-carboxylic
esters or 2,3-dicarboxylic esters (XLVII, Table 6), respectively. The corresponding acids are obtained by the alkaline saponification of the esters. Unlike the dihydrofuran-3-carboxylic acids, the dihydrothiophene-3-carboxylic acids are not readily decarboxylated; nor is it possible to add methanol to the double bond under normal conditions (14).

**TABLE 5**

**Products of the Rearrangement of α-Acyl-γ-thiolactones**

<table>
<thead>
<tr>
<th>XLIV</th>
<th>XLV</th>
<th>B.p. (°C/mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R¹</td>
<td>R²</td>
<td>Yield (%)</td>
</tr>
<tr>
<td>a H</td>
<td>CH₄</td>
<td>84</td>
</tr>
<tr>
<td>b CH₄</td>
<td>CH₄</td>
<td>73</td>
</tr>
<tr>
<td>c CO₂C₄H₈</td>
<td>C₅H₁₀</td>
<td>86</td>
</tr>
</tbody>
</table>

**TABLE 6**

**Products of the Rearrangement of α-Acyl-δ-thiolactones**

<table>
<thead>
<tr>
<th>XLVI</th>
<th>XLVII</th>
<th>B.p. (°C/mm Hg)</th>
<th>Lit. ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>R¹</td>
<td>R²</td>
<td>Yield (%)</td>
<td></td>
</tr>
<tr>
<td>a H</td>
<td>H</td>
<td>CH₃</td>
<td>82</td>
</tr>
<tr>
<td>b H</td>
<td>CH₄</td>
<td>CH₃</td>
<td>91</td>
</tr>
<tr>
<td>c H</td>
<td>CO₂C₄H₈</td>
<td>C₅H₁₀</td>
<td>83</td>
</tr>
<tr>
<td>d CH₄</td>
<td>H</td>
<td>C₅H₁₀</td>
<td>80</td>
</tr>
<tr>
<td>e CH₄</td>
<td>CH₄</td>
<td>CH₃</td>
<td>81</td>
</tr>
<tr>
<td>f CH₄</td>
<td>CO₂C₄H₈</td>
<td>C₅H₁₀</td>
<td>78</td>
</tr>
</tbody>
</table>

**Rearrangement of α-Acylactams**

In order to avoid the N-acylation of lactams during the course of the ester condensation, it is best to effect the reaction on N-alkylated or N-arylated lactams. The difficulties encountered during the condensation of lactams have been referred to earlier. The solvolysis of the amide linkage is an essential prerequisite in the rearrangement of α-ethoxalyl-N-methyl-γ-butyrolactam (11) in alcohol/H⁺. Ring stabilization of the cyclic carboxylic acid derivatives generally results from the acylation (see the section on optical measurements). α-Acylactones are less susceptible to hydrolysis than are the unsubstituted lactones. Since lactams are more resistant to alcoholysis than lactones, it follows that α-acyllac-
tams are particularly stable to proton-catalyzed alcoholysis. Thus no change worth mentioning is observed in the \( \alpha \)-acyl-\( \gamma \)-lactams (XLVIII) even after heating for 180 hr in ethanol containing 5% HCl. Though it is true that the UV absorption band at 301 \( \text{m}_{\mu} \) due to the acyl bond is diminished by 50-60% on boiling in absolute methanol/\( \text{H}_{2}\text{SO}_{4} \), no pyrrolidinecarboxylic esters (XLVIIIa) or pyrroline derivatives of type XLVIIIb could be isolated (11).

The amide linkage in \( \gamma \)-lactams is weakened by acylation with a strongly electronegative acyl group, such as the nicotinyl group (XLVIIIid).

The fission of the \( \alpha \)-nicotinyl-\( \gamma \)-lactams and their simultaneous decarboxylation is thus rendered possible by heating with concentrated HCl in a bomb tube. The ring-opened compound can be cyclized to the pyrrolidine (see p. 222). As in the case of the corresponding lactones, the \( \delta \)-lactams are also opened solvolytically more readily than are the \( \gamma \)-lactams. Thus \( \alpha \)-ethoxalyl-N-methyl-2-piperidone (XLIX) can be rearranged in boiling absolute ethanol/14% HCl (42); decarboxylation yields 2-carbethoxy-N-methyltetrahydropyridine (L) (42, 43).

The rearrangement to L involves the loss of one molecule of CO\(_2\). In order to explain the course of the reaction, it must be assumed that the lactam ring is partially opened hydrolytically by the water present, as a result of the equilibrium due to the high concentration of HCl in the reaction medium.

\[
\text{C}_2\text{H}_5\text{OH} + \text{HCl} \rightleftharpoons \text{C}_2\text{H}_5\text{Cl} + \text{H}_2\text{O}
\]

This results in the formation of a \( \beta \)-ketoacid (XLIXa) which has a low stability like oxalacetic acid, and is decarboxylated to give the amino-ketone XLIXb or hemiaminal XLIXc. Elimination of water stabilizes the latter as the tetrahydropyridinecarboxylic ester L.

We have reported earlier on similar conditions of decarboxylation and esterification (5) (see also sections on Rearrangement of \( \alpha \)-Acyl-\( \delta \)-lactones and Rearrangement in Aqueous Mineral Acid). Other rearrange-
mements undergone by α-acyllactams in boiling hydrochloric acid are also described in the section on rearrangement in mineral acid.

**Rearrangement of 4-Acyloxazolin-5-ones**

The process used by Cornforth for the synthesis of oxazolecarboxylic acids (44, 45) may be regarded as an original variant of the α-acyllactone rearrangement. When the sodium salts of the 4-hydroxyalkylideneoxazolin-5-ones (LI) are heated, the sodium salts of the 5-alkyloxazole-4-carboxylic acids (LII) are obtained. This method has been applied to various oxazoline derivatives (44, 46) (see Table 7).

The rearrangement of oxazolones in alcoholic hydrochloric acid gives no satisfactory results. Only 2-benzyl-4-hydroxymethyleneoxazolin-5-one (LIIb) rearranges in small yield in methanol/ethereal hydrochloric acid. The ester thus formed can be saponified with NaOH to give 2-benzyl-

<table>
<thead>
<tr>
<th>Table 7</th>
<th>Yields of 5-Alkyloxazole-4-carboxylic Acids (LII) Resulting from the Rearrangement of 4-Hydroxyalkylideneoxazolin-5-ones (LI) by the Method of Cornforth</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R¹</td>
</tr>
<tr>
<td>a</td>
<td>C₆H₅</td>
</tr>
<tr>
<td>b</td>
<td>C₆H₅—CH₃</td>
</tr>
<tr>
<td>c</td>
<td>C₆H₅—CH=CH</td>
</tr>
<tr>
<td>d</td>
<td>C₆H₅—CH=CH</td>
</tr>
<tr>
<td>e</td>
<td>C₆H₅—CH=CH</td>
</tr>
<tr>
<td>f</td>
<td>n-C₆H₁₁</td>
</tr>
<tr>
<td>g</td>
<td>C₆H₅—CH=CH</td>
</tr>
</tbody>
</table>
oxazole-4-carboxylic acid (LIIb) (47). Alcoholytic ring opening of the oxazolones (LI) causes the stabilization of the enolic γ-OH group as an acid amide group. With the exception of 2-benzyloxazolone, LIIb, no ring closure of this ketoester (LIA) in methanol/H⁺ to the oxazole-4-carboxylic ester (LIIA) could be observed (26). The cyclization of the open-chain acylaminoacetoacetic ester (LIA) can, however, be accomplished by heating with thionyl chloride or H₂SO₄/Ac₂O. Saponification of the oxazolecarboxylic esters (LIIA) with NaOH yields the oxazolecarboxylic acids (LII) (26).

\[
\begin{align*}
\text{L} & \quad \text{CH₃OH/H⁺} \quad \text{SOCl₂} \\
\text{L} & \quad \text{CO₂CH₃} \\
\text{L} & \quad \text{CO₂H} \\
\end{align*}
\]

The 4-phenylazo-2-phenyloxazolones can be rearranged in similar manner to the α-phenylazo-γ-lactones (XXX). Heating of LIII in methanol/20% KOH affords a high yield of 1,5-diphenyl-3-carboxy-1,2,4-triazole (LIIIA) (28). Tetrazolecarboxylic acids were obtained from 4-phenylazo-1,2,3-triazolones in corresponding manner (47a).

\[
\begin{align*}
\text{L} & \quad \text{CH₂OH/KOH} \quad 91\% \\
\text{L} & \quad \text{NO₂} \\
\text{L} & \quad \text{CO₂H} \\
\end{align*}
\]

Isoxazolecarboxylic acids are also accessible via the acyllactone rearrangement. Thus treatment of 3-phenyl-4-benzoylisoxazol-5-one (LIV) with concentrated NaOH yields 3,5-diphenylisoxazole-4-carboxylic acid (LIVA) (29). Phenylfurazancarboxylic acids are formed from 3-aryl-4-oximinoisoxazol-5-ones in an analogous manner (47b, 47c).

\[
\begin{align*}
\text{H₃C} & \quad \text{CO} \quad \text{C₄H₄} \\
\text{LIV} & \quad \text{1. conc. NaOH} \quad \text{2. HCl} \\
\text{H₃C} & \quad \text{COOH} \\
\end{align*}
\]

Rearrangement of α-Substituted α-Acylactones

Substitution by Means of Alkyl Halide

α-Hydroxyalkylidene-γ-lactones possess an additional acidic CH group in the α-position. The α-methylated lactones are obtained by heat-
ing under reflux with an excess of methyl iodide in absolute acetone (48). The method of Marshall and Cannon (benzene/dimethylformamide) also affords good yields (49).

The substitution of the \( \alpha \)-hydrogen atom fixes the \( \alpha \)-alkyl-\( \alpha \)-acyllactones LV in the keto form, and no enol reaction with FeCl\(_3\) is consequently observed. If LV (a–c) are heated for approximately 24 hr in absolute methanol containing 3\% HCl, the tetrahydrofurancarboxylic esters LVI are obtained.

\[
\begin{align*}
\text{LV (a–c)} & \quad \text{CH}_2\text{OH}/\text{H}^+ \\
\text{a: } R = \text{H} & \quad \text{b: } R = \text{CH}_3 & \quad \text{c: } R = \text{CO}_2\text{C}_2\text{H}_5
\end{align*}
\]

These examples show that even nonenolizable \( \alpha \)-acyllactones can be rearranged.

**Substitution via the Michael Addition**

\( \alpha \)-Acyllactones can react as \( \alpha \)-substituted \( \beta \)-dicarbonyl compounds by a Michael addition with \( \alpha \beta \)-unsaturated carbonyl compounds such as methyl vinyl ketone. The substituted \( \alpha \)-acyl-\( \gamma \)-lactones LVII (a–b) thus obtained rearrange to the tetrahydrofurancarboxylic esters LVIII (a–b) in methanol/\( \text{H}^+ \) (27).

\[
\begin{align*}
\text{LVII (a, b)} & \quad \text{CH}_2\text{OH}/\text{H}^+ \\
\text{a: } R = \text{H} & \quad \text{b: } R = \text{CO}_2\text{C}_2\text{H}_5
\end{align*}
\]

**Substitution by Coupling with Diazonium Salts**

\( \alpha \)-Acyllactones couple with diazonium salts in an aqueous medium. The acyl group is usually eliminated, and the azo compound is stabilized as the \( \alpha \)-hydrazone of the corresponding lactone. In some instances, however, the azo compound can be isolated. Thus the azo compound LIX is obtained by coupling \( \alpha \)-benzoylbutyrolactone (XXVI) with \( p \)-nitroanilinediazonium chloride (49a).

\[
\begin{align*}
\text{XXVI} & \quad \text{O}_2\text{N–C}_6\text{H}_4\text{–N}_2\text{Cl} \\
\text{pH = 3–4, CH}_3\text{OH/H}_2\text{O} & \quad \text{CO–C}_6\text{H}_4
\end{align*}
\]
Rearrangement of Special Acyllactones

The rearrangement of dilactones of type LXa (50), LXb (51), LXc (52) offers interesting synthetic possibilities.

Ester condensations do not proceed uniformly with these unstable lactones. The use of NaH as condensing agent affords the best yields, and the monoacyllactones (e.g. LXI) are formed (53). Rearrangement of LXI in ethanol/H⁺ results in the formation of a tetrahydrofuran ester lactone LXII, which is converted into the dihydrofuran derivative LXIII by distillation with polyphosphoric acid (53).

The condensation accompanied by the alcoholytic fission of the lactone ring of the spirolactone LXb with formic ester and sodium yields approximately 80% of the γ-ketopimelic acid half-ester LXIV, and only a small quantity of α-acyllactone which is difficult to separate from the by-products (53).

α-Acyllactones

The α-acyllactone rearrangement essentially also proceeds in water/H⁺. The rearrangement of acyllactones in both absolute alcohol/H⁺ and water/H⁺ involves the solvolytic fission of the lactone ring; the former case results in the trans-esterification of the lactonecarboxyl group, the
latter in the formation of the heterocyclic 3-carboxylic acid. This crystallizes out, so that the equilibrium is displaced in the direction of the rearrangement product. If the open-chain intermediate or the carboxylic acid readily loses CO₂, various decarboxylation products dependent on the acid concentration are obtained.

The rearrangement can usually be effected extremely simply. If α-hydroxymethylene-δ-lactones (LXVA–g) are dissolved in concentrated hydrochloric acid at 25°, the corresponding dihydropyran-3-carboxylic acids (LXVIa–g) are precipitated after some time as colorless crystals in yields of 80–90%.

The ester group in the α-hydroxymethylene-γ-carbethoxy-δ-lactones LXVf and g remains unsaponified, and the half-esters LXVIIf and g can be isolated.

\[ \text{R}^1 \text{OH} \text{R}^2 \text{R}^3 \xrightarrow{\text{H}_2\text{O}/{\text{H}^+}} \text{R}^1 \text{R}^2 \text{R}^3 \text{CO}_2\text{H} \]

Rearrangement of α-ethoxalyl-δ-caprolactone (LXVII) in concentrated hydrochloric acid yields the 6-methyl-5,6-dihydro-4H-pyran-2,3-dicarboxylic acid (LXVIII) or its half-ester (5).

\[ \text{CO}_2\text{C}_2\text{H}_4 \]

α-Acetyl-δ-lactones (LXIXa,b) dissolved in concentrated hydrochloric acid are decarboxylated even at room temperature and δ-chloroketones (LXXa,b) can be isolated. The rearrangement to the carboxylic acids LXXIa,b can, however, be accomplished in ice-cooled dilute hydrochloric acid.

\[ \xrightarrow{2\text{N HCl}} \]

\[ \text{R}^1 \text{R}^2 \text{R}^3 \xrightarrow{\text{conc. HC}l} \text{R}^1 \text{R}^2 \text{R}^3 \text{Cl} \]

\[ \text{R}^1 = \text{CH}_3, \text{R}^2 = \text{R}^3 = \text{H} \]
\[ \text{b: R}^1 = \text{R}^2 = \text{R}^3 = \text{CH}_3 \]

\[ \text{R}^1 = \text{R}^2 = \text{R}^3 = \text{H}, \text{R}^4 = \text{CO}_2\text{C}_2\text{H}_4 \]
\[ \text{g: R}^1 = \text{R}^2 = \text{H}, \text{R}^3 = \text{C}_8\text{H}_5 \]
The long-known conversion of dehydroacetic acid (LXXII) in concentrated hydrochloric acid into 2,6-dimethyl-γ-pyrone (LXXIIa) \( (54) \), is also an example of an acyllactone rearrangement in \( \text{H}_2\text{O}/\text{H}^+ \).

\[
\begin{align*}
\text{LXXII} & \xrightarrow{\text{conc. HCl}} \text{LXXIIa} \\
\end{align*}
\]

This rearrangement is also undergone in ethanol/\( \text{H}^+ \). The course of the reaction is explained below.

The conversion, discovered by Wiley, of 3-cinnamoyl-4-hydroxy-6-methyl-2-pyrone (LXXIII) into the γ-pyrone derivative LXXIIIa is an example of the rearrangement of lactones containing unusual acyl groups \( (55) \).

\[
\begin{align*}
\text{LXXIII} & \xrightarrow{12\text{N HCl}} \text{LXXIIIa} \\
\end{align*}
\]

The rearrangement of a β-acyl-Δ-lactone is described by Lawson \( (55a) \). If 4-acetyl-3,4-dihydrocoumarin (LXXIIIb) is heated for 1 hr in \( 3\text{N} \) hydrochloric acid, 2-methylbenzoferan-3-acetic acid (LXXIIIc) is formed.

\[
\begin{align*}
\text{LXXIIIb} & \xrightarrow{3\text{N HCl} \ 1\text{ hr}} \text{LXXIIIc} \\
\end{align*}
\]

No further examples of the rearrangement undergone by β-acyllactones are available as yet, due to the difficulties encountered in the preparation of these compounds.

The rearrangement of α-hydroxyalkylidene-γ-lactones (LXXIV) yields only small quantities of dihydrofuran-3-carboxylic acids, as these are very readily decarboxylated in aqueous mineral acids. γ-Hydroxyketones (LXXIVA) are obtained instead, and these can be identified as their 2,4-dinitrophenylhydrazones \( (5,22) \).

\[
\begin{align*}
\text{LXXIV} & \xrightarrow{\text{H}_2\text{O}/\text{H}^+} \text{LXXIVA} \\
\end{align*}
\]
α-Acetyl-γ-lactones (LXXVa–c) are decarboxylated in concentrated hydrochloric acid at room temperature (5), resulting in good yields of γ-chloroketones (LXXVIa–c).

\[
\begin{array}{c}
\text{LXXV (a–c)} \\
\text{a: } R_1 = R_2 = H \\
\text{b: } R_1 = \text{CH}_3, R_2 = H \\
\text{c: } R_1 = R_2 = \text{CH}_3
\end{array}
\]

α-Substituted α-acetylactones will also undergo a rearrangement in aqueous acids. If α-chloro-α-acetylbutyrolactone (LXXVII) is heated with conc. HCl, loss of CO₂ results in the formation of a hemiketal LXXVIII in equilibrium with the open-chain chloroketoalcohol, LXXVIIIa (56). Stevens (57) was able to show that the hemiketal, LXXVIII, partially condenses with the alcohol LXXVIIIa to give the ketal LXXIX. A patent specification by Klingendruss (58) describes a "saponification" of compound LXXVII, effected by warming in ethanol/H₂SO₄ at 50°, to the ketal LXXX. The formation of the 2-alkoxytetrahydrofurans is in agreement with the results obtained in the rearrangement of other α-acyl-γ-lactones (see above).

Furan-3-carboxylic acids are less readily decarboxylated than dihydrofuran-3-carboxylic acids. β,γ-Unsaturated α-acyllactones can consequently readily be converted into furancarboxylic acids by means of aqueous acid, as illustrated by the trouble-free conversion of α-acetylangelica lactone (LXXXI) into pyrotritaric acid (LXXXIa). Vigorous reaction conditions will, however, also cause decarboxylation to acetonylacetone (LXXXIb) in this instance (59).
The isocarbopyrotritaric acid (LXXXII) yields a furandicarboxylic acid LXXXIIa (carbopyrotritaric acid) (60).

![Chemical structure of isocarbopyrotritaric acid and its rearranged product](image)

A similar reaction is undergone by 3-acetyl-5-phenyl-3H-2-furanone (LXXXIII), which is rearranged to 2-methyl-5-phenylfuran-3-carboxylic acid (LXXXIIIa) (61).

![Chemical structure of 3-acetyl-5-phenyl-3H-2-furanone and its rearranged product](image)

α,β-Unsaturated α-acetyllactones also rearrange in yields of over 90% to furan-3-carboxylic acids, as shown by examples LXXXIV–LXXXIVa and LXXXV–LXXXVa (62).

![Chemical structures of α,β-unaturated α-acetyllactones and their rearranged products](image)

In this reaction, the double bond is displaced into the β,γ-position. If the γ-position in the α-acetyllactone is blocked by a tertiary grouping, as e.g., in 2,2,3-trimethyl-4-acetyl-5-furanone (LXXXVI), no furan-carboxylic acid can be formed (8).

![Chemical structure of 2,2,3-trimethyl-4-acetyl-5-furanone](image)

The formation of the dihydroxyfuran LXXXVIII from the α-chloro-acetyl-α-methyl-γ-butyrolactone LXXXVII (63) demands a special reaction mechanism (see the section on optical measurements). Essentially, however, this is also an example of an acyllactone rearrangement.

![Chemical structures of α-chloro-acetyl-α-methyl-γ-butyrolactone and its rearranged product](image)
THE ACYLLACTONE REARRANGEMENT

An interesting reaction undergone by the "dibutolactones" [α-(2-tetrahydrofurylidene)-γ-hydroxybutyrolactones, LXXXIX] was reported by Fittig as long ago as 1892 (64). On heating in dil. HCl they yield spiro compounds of the type XC by decarboxylation. Fittig called this class of compounds "oxetones."

$$\begin{align*}
\text{LXXXIX} & \quad \xrightarrow{\text{dil. HCl, Heat}} \quad \text{XC} \\
\text{R} & = \text{H, CH}_2, \text{C}_6\text{H}_5
\end{align*}$$

Dibutolactone may be considered as an α-acyllactone stabilized in the enol form. The formation of the oxetones is thus also an example of an acyllactone rearrangement.

α-ACYLTHIOLACTONES

The action of conc. HCl on the α-hydroxyalkylidene-δ-thiolactones, XCI, results in the formation of the dihydrothiopyranecarboxylic acids XCII; these thus become readily accessible via this simple reaction (65). The rearrangement of α-acetyl-δ-thiolactone is completed after only a few minutes. The dicarboxylic acid XCIIc is present in the reaction mixture as the anhydride.

$$\begin{align*}
\text{XCI (a-c)} & \quad \xrightarrow{\text{conc. HCl}} \quad \text{XCII (a-c)} \\
a: R = \text{H} & \quad b: R = \text{CH}_3 & \quad a: R = \text{H} & \quad b: R = \text{CH}_3 \\
c: R = \text{CO}_2\text{C}_6\text{H}_5 & \quad c: R = \text{CO}_2\text{H}
\end{align*}$$

Of the α-acyl-γ-thiolactones, only the α-ethoxalyl compound, XCIIIc, rearranges in good yield. In the case of the α-hydroxymethylene- and α-acetylthiolactones XCIIIa and b, the yield of dihydrothiophenecarboxylic acids is reduced by a retrogressive ester condensation (acid cleavage) and partial decarboxylation (ketonic cleavage). Compounds XCIVa–b are obtained more easily by rearrangement in alcohol/H⁺ followed by the saponification of the esters.

$$\begin{align*}
\text{XCIII (a-c)} & \quad \xrightarrow{\text{H}_2\text{O/H}^+} \quad \text{XCIV (a-c)} \\
a: R = \text{H} & \quad b: R = \text{CH}_3 & \quad a: R = \text{H} & \quad b: R = \text{CH}_3 \\
c: R = \text{CO}_2\text{C}_6\text{H}_5 & \quad c: R = \text{COOH}
\end{align*}$$
**α-Acylactams**

The hydrolytic ring opening of α-acylactams can be effected either by heating with conc. HCl in a bomb tube at 130° or by boiling under reflux, when decarboxylation takes place. Various examples of this reaction are described in the literature (66). Späth and Bretschneider applied this method to the synthesis of nicotine (18). The recycelization to the heterocycle is however not always achieved under the conditions of the rearrangement. This can then be effected via an indirect method: N-methylpyrrolidone is condensed with nicotinic ester to the α-acylactam XCV, which is hydrolyzed to XCVa with HCl in a bomb tube. The carbonyl group is reduced and the alcohol formed converted into the alkyl iodide XCVb, which then cyclizes to DL-nicotine (XCVI) with the elimination of HI.

\[
\begin{align*}
\text{O} & \quad \text{conc. HCl} \\
\text{CH}_3 & \quad 130^\circ \quad \text{CO}_2 \\
\text{XCV} & \quad 1. \text{Reduction} \\
& \quad \text{2. HI} \\
\text{NH} & \quad \text{XCVb} \\
\text{XCVa} & \quad \text{CH}_3 \\
\text{XCV} & \quad \text{H} \quad \text{I} \\
\text{XCVa} & \quad \text{N} \quad \text{CH} \\
\text{XCVI} & \quad \text{N} \quad \text{CH} \\
\end{align*}
\]

The synthesis of myosmine (XCVII) proceeds along similar lines (67). In this instance, ring opening, debenzoylation, and recycelization occur when α-nicotinyl-N-benzoyl-2-pyrrolidone is heated in conc. HCl; the detour via the iodide consequently becomes superfluous. α-Acylpiperidones can also be opened in boiling conc. HCl. The fission is then accompanied by the simultaneous rearrangement to the tetrahydropyridine; this reaction also agrees with the scheme of the acyllactone rearrangement accompanied by the loss of CO₂ and H₂O. The tetrahydropyridine ring is readily hydrogenated to piperidine. The synthesis of DL-anabasine (XCVIII→XCIX) is an example of this type of rearrangement (68). In the meantime, the rearrangement of various α-acyl-N-methylpiperidones to the corresponding piperideine derivatives was also accomplished (13).
Rearrangement in Higher Alcohols

\(\alpha\)-Acyllactones can essentially also be rearranged in the presence of higher alcohols (69). \(\alpha\)-Hydroxymethylene lactones (XXIVa or XIIIa) thus yield the corresponding tetrahydro- and dihydrofuran- or pyran-carboxylic esters, respectively, of propanol to \(n\)-octanol.

Besides the normal products the rearrangement in sec-butanol also results in the partial formation of the enol ether, C, which rearranges to dihydropyran-3-carboxylic acid in conc. HCl.

Rearrangement in benzyl alcohol gives 2-benzyloxytetrahydropyran-3-carboxylic acid benzyl esters (CI) (69).

Enol Content of the \(\alpha\)-Acyllactones

The degree of enolization of acyllactones has recently been reported (30, 70). The reason for the large differences in the enol content of individual acyllactones may be attributed to steric effects, and is not solely conditioned by the branching of the \(\alpha\)-substituents (71) or the alcohol components (72). No relationship could be determined between the enolizing tendency and the course of the rearrangement.
Optical Measurements of \( \alpha \)-Acylactones, -thiolactones, and -lactams and Their Rearrangement Products

UV Spectra

Together with the enol reaction with \( \text{FeCl}_3 \), UV absorption measurements have proved valuable in the detection and especially the quantitative determination of \( \alpha \)-acylcyclocarboxylic acid derivatives. The UV spectra of all the \( \alpha \)-acyl compounds which we have synthesized are given in the original papers (2). The increase in mesomerism due to the introduction of the acyl groups into the lactones, thiolactones, and lactams results in a bathochromic shift of the main maxima in the UV range (73). The shifts associated with the formyl, acetyl, and ethoxalyl groups amount to approximately 30–40, 50–60, and 65–75 \( \text{m}\mu \), respectively. A number of examples are shown in Table 8.

**Table 8**

<table>
<thead>
<tr>
<th>Compound</th>
<th>( R )</th>
<th>( \lambda_{\text{max}} ) (m( \mu ))</th>
<th>( \log \varepsilon )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{H}_2\text{C} \text{O} \text{C} \text{OH} )</td>
<td>( \text{H} )</td>
<td>212</td>
<td>1.78</td>
</tr>
<tr>
<td>( \text{H}_2\text{C} \text{O} \text{C} \text{R} )</td>
<td>( \text{CH}_3 )</td>
<td>252</td>
<td>3.97</td>
</tr>
<tr>
<td>( \text{N} \text{O} )</td>
<td>( \text{CO}_2\text{C}_2\text{H}_5 )</td>
<td>282</td>
<td>3.91</td>
</tr>
<tr>
<td>( \text{N} \text{O} )</td>
<td>( \text{CH}_3 )</td>
<td>206</td>
<td>3.75</td>
</tr>
<tr>
<td>( \text{S} \text{O} )</td>
<td>( \text{H} )</td>
<td>237</td>
<td>3.61</td>
</tr>
</tbody>
</table>

UV absorption is also used to advantage in the quantitative determination of the dihydropyrans or dihydrofurans, which are formed in equilibrium with the tetrahydro compounds during the rearrangement.
Table 9 shows a few examples of the position of the absorption maxima of the dihydropyran carboxylic esters and their S and N homologs.

**TABLE 9**
Position of the UV Absorption Maximum and Extinction Coefficient of a Few 5,6-Dihydropyran-3-carboxylic Acid Esters and the Corresponding Thiopyran and Pyridine Derivatives

<table>
<thead>
<tr>
<th>Compound</th>
<th>R</th>
<th>( \lambda_{\text{max}} ) (m(\mu))</th>
<th>( \log e )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H,C(\text{O})R'</td>
<td>a</td>
<td>H</td>
<td>240</td>
</tr>
<tr>
<td></td>
<td>b</td>
<td>CH(_3)</td>
<td>248</td>
</tr>
<tr>
<td></td>
<td>c</td>
<td>CO(_3)C(_2)H(_4)</td>
<td>245</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-</td>
<td>273</td>
</tr>
<tr>
<td>N,C(\text{O})C(_2)H(_4)</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>a</td>
<td>H</td>
<td>.281</td>
</tr>
<tr>
<td></td>
<td>b</td>
<td>CH(_3)</td>
<td>281</td>
</tr>
<tr>
<td></td>
<td>c</td>
<td>CO(_3)C(_2)H(_4)</td>
<td>289</td>
</tr>
</tbody>
</table>

The bathochromic shift undergone by the maxima of the dihydro-thiopyran carboxylic esters is explained by the greater contribution to the mesomeric system made by the electron pairs of sulfur compared to those of oxygen or nitrogen \((14,15)\). The increased ring-stability of the \(\alpha\)-acyllactones compared to the unsubstituted lactones is demonstrated by kinetic measurements. Whereas, e.g. the band at 237 m\(\mu\) in unsubstituted \(\delta\)-thiolactone in methanol/NaOH at room temperature disappears within one minute as a result of ring fission, about \(\frac{1}{3}\) of the original amount of \(\alpha\)-acyl-\(\delta\)-thiolactone is still unchanged after 7 hr under the same conditions. [See refs. \((14,15)\).]

**IR Spectra**

The IR spectra of weakly enolized \(\alpha\)-acyllactones possess two characteristic separate C=O bands (lactone and acylcarbonyl group, respectively) and a C=C double bond band around 1650 cm\(^{-1}\) which is attributable to the enol constituent. A few examples are given in Table 10.

**TABLE 10**
IR Absorption Maxima of a Few \(\alpha\)-Acyll-\(\gamma\)-lactones

<table>
<thead>
<tr>
<th>Compound</th>
<th>C=O (Lactone) (cm(^{-1}))</th>
<th>C=O (Acyl) (cm(^{-1}))</th>
<th>C=C (Enol) (cm(^{-1}))</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\alpha)-Acetyl-(\gamma)-butyrolactone</td>
<td>1766</td>
<td>1720</td>
<td>1650</td>
<td>Film</td>
</tr>
<tr>
<td>(\alpha)-Acetyl-(\gamma),(\gamma)-dimethyl-(\gamma)-butyrolactone</td>
<td>1763</td>
<td>1720</td>
<td>1650</td>
<td>Film</td>
</tr>
<tr>
<td>(\alpha)-Ethoxalyl-(\gamma)-butyrolactone</td>
<td>1750</td>
<td>1710(^a)</td>
<td>1650</td>
<td>in CCl(_4)</td>
</tr>
</tbody>
</table>

\(^a\) CO Frequency of the COOC\(_2\)H\(_4\) group.
In the case of \( \alpha \)-acyl compounds with a high enol content, the band due to the acyl C=O group disappears, while the position of the lactone carbonyl band is shifted to lower frequencies, as is invariably observed with \( \alpha, \beta \)-unsaturated esters and lactones. We have recently reported on the position of the frequency of endocyclically unsaturated lactones (74). As a result of chelation, the enolic OH band is similarly displaced and coincides in part with the CH\(_2\) valency vibrations (Table 11).

<table>
<thead>
<tr>
<th>Compound</th>
<th>O=H (Enol) (cm(^{-1}))</th>
<th>C=O (Lactone) (cm(^{-1}))</th>
<th>C=C (cm(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \alpha )-Hydroxymethylene-6-caprolactone</td>
<td>2750</td>
<td>1680</td>
<td>1615</td>
</tr>
<tr>
<td>( \alpha )-Hydroxymethylene-( \beta )-methyl-6-caprolactone</td>
<td>2750</td>
<td>1665</td>
<td>1615</td>
</tr>
</tbody>
</table>

The carbonyl bands of the \( \gamma \)- and \( \delta \)-thiolactones, 1705 and 1665 cm\(^{-1}\), respectively, are shifted by about 70 cm\(^{-1}\) towards lower frequencies compared to the \( \gamma \)- and \( \delta \)-lactones (1774 and 1735 cm\(^{-1}\), respectively); those of the \( \alpha \)-ethoxalylthiolactones are located approximately 30 cm\(^{-1}\) lower still (Table 12).

<table>
<thead>
<tr>
<th>Compound</th>
<th>C=O (COOC(_2)H(_5) group) (cm(^{-1}))</th>
<th>C=O (Lactone) (cm(^{-1}))</th>
<th>C=C (Enol) (cm(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \gamma )-Thiobutyrolactone</td>
<td>-</td>
<td>1705</td>
<td>-</td>
</tr>
<tr>
<td>( \delta )-Thiovalerolactone</td>
<td>-</td>
<td>1665</td>
<td>-</td>
</tr>
<tr>
<td>( \alpha )-Ethoxalyl-( \gamma )-thiobutyrolactone</td>
<td>1725</td>
<td>1682</td>
<td>1825</td>
</tr>
<tr>
<td>( \alpha )-Ethoxalyl-( \delta )-thiovalerolactone</td>
<td>1730</td>
<td>1638</td>
<td>1590</td>
</tr>
</tbody>
</table>

The 2-hydroxypyrans (CIV), both in KBr and chloroform solution, exhibit a sharp OH band in the IR at 3425 or 3460 cm\(^{-1}\), respectively. Even in the solid state no OH association occurs, which points to steric hindrance of the OH group. This explains why no ketalization of the 2-hydroxypyrans CIV is observed during the rearrangement of primary and secondary \( \alpha \)-ethoxalyl-\( \delta \)-lactones.

![Diagram](https://via.placeholder.com/150)
Ring-Opening Mechanism of the $\alpha$-Acyl-$\delta$-lactones

Whereas rearrangement of primary and secondary $\alpha$-ethoxalyl-$\delta$-caprolactones (CIII) in absolute alcohol/HCl results in the formation of 2-hydroxytetrahydropyran derivatives (CV), the tertiary $\alpha$-ethoxalyl-$\beta,\delta$-dimethyl-$\delta$-caprolactone (CVIa) yields a 2-methoxytetrahydropyran derivative CVId (see section on rearrangement of $\alpha$-acyl-$\delta$-lactones, particularly Table 2). This difference in reaction course can be explained by the different mechanisms of alcoholysis undergone by the lactones (30).

While primary and secondary $\alpha$-acyllactones are opened by acyl-oxy fission, the opening of tertiary lactones is effected by alkyl-oxy fission. The strongly electrophilic carbonium ion, CVIC, formed in the latter case can stabilize itself with alcohol to the 2-alkoxytetrahydropyran, CVId.

The acyl-oxy fission mechanism, on the other hand, converts CIII into a 2-hydroxy product, CV; ketal formation of the latter to a 2-methoxy compound cannot take place as a result of steric hindrance (IR spectra, molecular models) due to the presence of the neighboring bulky carboxy groups (30).

In the planar tetrahydrofuran ring, a 2-hydroxy group is no longer sterically hindered. Rearrangement of the ethoxalyl-$\gamma$-lactones consequently yields 2-methoxytetrahydrofurans exclusively. Nothing more can be concluded here from the rearrangement products concerning the ring-opening mechanism.
Mechanism of the Rearrangement

No common reaction mechanism can be established experimentally, nor can this be expected when so many equilibria are possible. Examples of possible rearrangement mechanisms are given in the following sections.

In Alcohol/H⁺

If α-hydroxymethylene-γ-lactones are dissolved in methanol, the absorption at 240 mµ due to the acyllactone drops to an equilibrium value. This phenomenon can be explained by the formation of a hemiacetal. Wislicenus determined the reduction in enol content of formylphenyl-acetic ester per unit time by titration according to the method of K. H. Meyer and isolated the hemiacetal formed (75). We consequently assume the following reaction stages:

Whether the formation of the hemiacetal or hemiketal occurs before or after the transesterification of the lactone cannot be determined. It is more probable that the hemiacetal formation initiates the rearrangement, since this increases the resonance stabilization of the acyllactone ring, thus facilitating its alcoholysis.

In H₂O/H⁺

The lactone ring A is opened by hydrolysis in aqueous acid. This results in the formation of a β-keto-γ- or δ-hydroxyacid B which either stabilizes itself as the heterocyclic carboxylic acid C or is decarboxylated to the ketoalcohols C'. In high concentrations of HCl, the OH group can be replaced by chlorine.
In the case of dehydroacetic acid, CVII, decarboxylation is followed by stabilization to the γ-pyrone ring (CVIII) (5).

**Special Mechanisms**

The rearrangement of α-chloroacetyl-α-methyl-γ-butyrolactone (CIX) follows a special reaction course. In this instance too, the lactone ring is first opened by hydrolysis. For the further course of the reaction, Huffman and Tarbell (49) propose a mechanism involving an allylic rearrangement, as was postulated by Stevens and Lenk (76) for a similar case of hydrolysis of an α-haloketone. This would explain the formation of 2,3-dihydroxy-2,3-dimethyltetrahydrofuran (CX).
Lacey (19) suggests the following mechanism for the rearrangement of $\alpha,\beta$-unsaturated $\gamma$-lactones (A):

Addition of a proton to the lactone group (B) yields an onium ion C via a kind of Saytzeff elimination; loss of the C$_5$-proton from C results in the formation of the complex D, followed by stabilization as the furancarboxylic acid E. This mechanism appears rather questionable to us as representative of rearrangements in an anhydrous medium, e.g. with BF$_3$ etherate. For the rearrangements in conc. HCl/acetic acid effected by Lacey, the hydrolysis of the acyllactone proposed in the preceding section appears more probable.

The rearrangement of the hydroxyalkylideneoxazolones A, which takes place by heating the Na salts at 200-300° according to the method of Cornforth, may be envisaged as proceeding via an oxonium structure, B. The thermal dissociation of the enol salt is followed by the formation of the oxonium salt B; alkyl-oxy fission opens the latter to a zwitterion, C, which stabilizes itself as the oxazolocarboxylic acid, D.

Limitations of the Rearrangement with Respect to the Ring Size and the Functional Groups

Ring Size

The application of the rearrangement to the preparation of macrocyclic ethers is hindered by the difficulties attendant on the synthesis of macrocyclic acyllactones. Even $\beta$-propio lactone undergoes no ester condensation, with the result that the rearrangement is thus far restricted to the synthesis of five- and six-membered ring heterocycles.
Functional Groups

The following functional groups are essential for the ring closure to the heterocycle in the rearrangement of five- and six-membered \( \alpha \)-acyllactones (thiolactones and -lactams).

1. An alcoholic or enolic OH group in the \( \gamma \)- or \( \delta \)-position.
2. A carbonyl group activated by an \( \alpha \)-carboxyl group. In rearrangements effected in alcohol/H\(^+\), this carbonyl group can also be present as the acetal or ketal (see preceding section).

If one of these groups is either absent or replaced by another active group, ring closure does not occur. If, for example, the OH group is replaced by an activated double bond (CXI) the rearrangement only yields the open-chain acetal CXII (77, 78).

If the carbonyl group is replaced by an activated double bond (CXIII), the lactone is merely transesterified and the open-chain ethylidene compound CXIV is obtained.

Replacement of the carbonyl by an OH group (CXV) similarly yields merely the open-chain hydroxyester CXIV (77).

Application of the \( \alpha \)-Acyllactone Rearrangement to Special Syntheses

During the investigations into the constitution of gentiopierin, the hemiacetallactones CXVIII (31) and CXI (79) were discussed in relation to its skeleton. The synthesis of the tetrahydropyran ring of these bicyclic lactones from the corresponding substituted \( \alpha \)-hydroxymethyl-enelactones (e.g., LXVI) was accomplished with the aid of the \( \alpha \)-acyllactone rearrangement.
The bicyclic lactone was obtained from the 1-alkoxy-6-isopropyltetrahydropyran-3-carboxylic acid (CXVII) by the Arndt-Eistert synthesis and ring closure via dihydropyranacetic acid.

Aminopyrans (CXX and CXXa) and aminofurans (CXXI) (23, 80) can be synthesized via the dihydropyran esters, readily obtainable by the rearrangement.

\[ \text{o-Ethylphenyl-3-tetrahydrofuryl ketone (CXXII) is obtained from } \alpha \text{-erythroidine by a repeated Hofmann degradation. Boekelheide and Morrison (81) have recently described a synthesis of the degradation product, in which } \alpha \text{-hydroxymethylenebutyrolactone was rearranged to tetrahydrofuran-3-carboxylic ester, which was then allowed to react with } o \text{-ethylphenyllithium to give the ketone CXXII.} \]

With a view to synthesizing muscarine, Eugster (82) also obtained 5-ethyldihydrofuran-3-carboxylic ester (CXXIII) by the application of the acyllactone rearrangement.

In connection with work on a synthesis of vitamin E, 2-heptadecyl-4,6,7-trimethyl-5-hydroxycoumarone-3-carboxylic ester (CXXV) was ob-
tained by the rearrangement of a 3-stearoylisocoumaranone (CXXIV) by English authors (88).

![Chemical structure](image)

**Conclusion**

The examples given illustrate the great reactivity of the α-acyl-lactones and the general applicability of the rearrangement reaction. It renders five- and six-membered heterocyclic 3-carboxylic acids or their decarboxylation products readily accessible. It is interesting to note in this context the occurrence of the dihydropyran-3-carboxylic acid grouping in natural products, such as in the py-tetrahydroserpentine derivative class of compounds, to which ajmalicine and other rauwolfia alkaloids belong.

It is not impossible that the biosynthesis of these compounds proceeds via α-acyllactones.

**Experimental**

**Preparation of the α-Acyl Compounds**

α-Hydroxymethylene-δ-caprolactone (7). A solution of δ-caprolactone (145 gm, 1.27 mole) and ethyl formate (103 gm, 1.40 mole) in absolute ether (700 ml) is added dropwise over a period of 2 to 3 hr to a stirred suspension of powdered sodium (30.8 gm, 1.33 gm atom) in absolute ether (300 ml) containing absolute ethanol (3 ml); a cream-colored sodium salt is formed. After being allowed to stand overnight the mixture is decomposed with ice-water and the ethereal solution separated; the aqueous phase is freed from ether under vacuum, treated with animal charcoal, filtered, and acidified in the cold with dilute hydrochloric acid (pH 3.8–3.2) with stirring. Crystalline α-hydroxymethylene-δ-caprolactone separates. It is filtered, washed with ice-water, and dried *in vacuo*. Yield 148 gm, 82%. Recrystallization from acetone-water and hot water affords colorless needles, m.p. 108°. FeCl₃ reaction in water: violet.

α-Ethoxalyl-δ-thiovalerolactone (8). Diisopropylamine (35.4 gm, 0.35 mole) in absolute ether (100 ml) is added dropwise to a Grignard solution consisting of magnesium turnings (8.2 gm, 0.35 gm atom) and ethyl bromide (38.2 gm, 0.35 mole) in absolute ether (120 ml) at such a rate that the ether boils gently. The reaction liquid becomes cloudy, then pale
gray and viscous. This is cooled to below $-10^\circ$ with an ice-salt mixture and \(\delta\)-thiovalerolactone (34.8 gm, 0.3 mole) and diethyl oxalate (73 gm, 0.5 mole) in absolute ether (150 ml) added dropwise with stirring. The viscous reaction mixture becomes orange-yellow. Stirring is continued for 12 hr, conc. HCl (55 ml) and ice-water (150 ml) added with cooling, and the mixture repeatedly extracted with ether. The combined ether extracts are dried over Na\(_2\)SO\(_4\), the ether evaporated and the crude product repeatedly fractionated \textit{in vacuo}, yielding a pale yellow oil (48 gm, 74%), b.p. 111–113°/0.1 mm. FeCl\(_3\) reaction in methanol-water: blue. UV spectrum: \(\lambda_{\max 1} 312\,\text{m}\mu\), loge 3.79; \(\lambda_{\max 2} 208\,\text{m}\mu\), loge 3.56.

\(\alpha\)-Acetyl-\(\beta\)-methyl-\(\delta\)-caprolactone (30). \(\beta\)-Methyl-\(\delta\)-caprolactone (52 gm, 0.4 mole) and absolute ethyl acetate (44 gm, 0.5 mole) are added dropwise to a stirred suspension of finely powdered sodium hydride (14.4 gm, 0.6 mole) in absolute ethyl acetate (176 gm, 2 moles) at room temperature. The reaction is initiated by gentle warming, and is then maintained at 5–10° by external cooling. The NaH goes into solution. After 24 hr the solution is treated with ice-water (250 ml) and extracted with ether (150 ml). The cooled aqueous layer is acidified to pH 3 with dilute hydrochloric acid and extracted four times with ether (120 ml portions). The combined ether extracts are briefly washed once with water and dried over Na\(_2\)SO\(_4\). Evaporation of the ether leaves an oil which is fractionally distilled \textit{in vacuo}, yielding a small quantity of acetoacetic ester (red enol reaction with FeCl\(_3\) in 50% methanol) b.p. 35–38°/0.05 mm, and colorless \(\alpha\)-acetyl-\(\beta\)-methyl-\(\delta\)-caprolactone (19 gm, 28%), b.p. 68–70°/0.05 mm. FeCl\(_3\) reaction in 50% methanol: violet. UV spectrum: \(\lambda_{\max 1} 262\,\text{m}\mu\), loge 3.9; \(\lambda_{\max 2} 204\,\text{m}\mu\), loge 3.2.

Rearrangements

\textbf{In methanol at 20° (7).} \(\alpha\)-Hydroxymethylene-\(\delta\)-caprolactone (118 gm) is dissolved in absolute methanol (1200 ml) containing HCl (3.4%) and allowed to stand for 48 hr at room temperature. The solution is then stirred into an excess of potassium carbonate solution and the 2-methoxy-3-carbomethoxy-6-methyltetrahydropyran extracted with ether. Distillation under vacuum yields a colorless oil (125 gm, 80%), b.p. 43–44°/0.05 mm. UV spectrum: \(\lambda_{\max} 240\,\text{m}\mu\), \(\alpha 15.8\) (84); the product accordingly contains 17.9% of 3-carbomethoxy-6-methyl-5,6-dihydro-4H-pyran (\(\alpha 88.5\)).

\textbf{In benzyl alcohol at 20° (69).} \(\alpha\)-Hydroxymethylene-\(\delta\)-caprolactone (10 gm) is allowed to stand in absolute benzyl alcohol (100 ml) containing HCl (4.3%) for 96 hr at room temperature and the solution stirred into a solution of K\(_2\)CO\(_3\) (400 ml, 10%). The work-up is identical to that for the reaction in methanol. The crude 2-benzoxy-6-methyltetrahydro-
pyran-3-carboxylic acid benzyl ester absorbs at $\lambda_{\text{max}}$ 240 $\mu\text{m}$, $\alpha6.8$ (and $\lambda_{\text{max}}$ 210 $\mu\text{m}$) and contains accordingly 11.5% of 6-methyl-5,6-dihydro-4H-pyran-3-carboxylic acid benzyl ester ($\lambda_{\text{max}}$ 240 $\mu\text{m}$, $\alpha59$). Repeated fractionation affords the pure saturated compound (20 gm, 84%), b.p. 150–151°/0.05 mm.

In octanol at 20° (69). $\alpha$-Hydroxymethylene-$\gamma$-caprolactone (15 gm) is dissolved in absolute n-octanol/4%HCl (150 ml) and allowed to stand for 10 days at room temperature, when the solution is stirred into a solution of $\text{K}_2\text{CO}_3$ (400 ml, 10%). The work-up is identical to that described for the reaction in methanol, and 2-octyloxy-6-methyltetrahydropyran-3-carboxylic acid octyl ester (34 gm, 89%) is obtained. The crude oil ($\lambda_{\text{max}}$ 240 $\mu\text{m}$, $\alpha9.4$) contains 16% of 6-methyl-5,6-dihydro-4H-pyran-3-carboxylic acid octyl ester ($\alpha59$). Repeated fractionation in vacuo affords the pure tetrahydrofuran ester, b.p. 145–146°/0.05 mm.

In methanol/$H^+$ under reflux (4). A solution of $\alpha$-methoxalyl-$\gamma$-butyrolactone (151.8 gm) in absolute 1$N$ HCl/methanol (1200 ml) is heated for 14 hr under reflux; the solution is allowed to stand for 3 days at room temperature and then stirred into an excess of potassium carbonate in water (2000 ml), so that the solution remains permanently alkaline. The solution is extracted 8 times with ether (150 ml portions) and the combined extracts washed twice with water (300 ml portions). The ethereal solution is dried over MgSO$_4$, the solvent evaporated and the residual oil fractionated in vacuo, yielding 2-methoxytetrahydrofuran-2,3-dicarboxylic acid dimethyl ester (96.6 gm, 54%), b.p. 72–73°/0.03 mm, as a colorless oil which slowly crystallizes partially on standing.

In conc. HCl at 20° (5, 8). $\alpha$-Hydroxymethylene-$\delta$-caprolactone (9) (100 gm) is suspended in concentrated hydrochloric acid (300 ml) and stirred for 3 hr. The dihydropyranecarboxylic acid formed is filtered off and the mother liquors are diluted with an equal volume of water and stored for 24 hr at 0°, when a further crop of the acid crystallizes. The crystals are washed with ice-water and dried, yielding colorless crystals of 6-methyl-5,6-dihydro-4H-pyran-3-carboxylic acid (91 gm, 91%), m.p. 114–116°, $\lambda_{\text{max}}$ 236 $\mu\text{m}$, log $\epsilon$ 4.06. More pyrancarboxylic acid can be isolated by extracting the mother liquors with ether.

If $\alpha$-acetyl-3-thiovalerolactone (10 gm) is dissolved in conc. HCl (40 ml), 2-methyl-5,6-dihydro-4H-thiopyran-3-carboxylic acid begins to crystallize within a few minutes. The mixture is allowed to stand for 1 hr at 0°, is diluted with $H_2O$ (40 ml) and the colorless carboxylic acid filtered on a glass frit. Yield 8.9 gm (89%), m.p. 130°, $\lambda_{\text{max}}$ 280 $\mu\text{m}$, log $\epsilon$ 4.06.

$\alpha$-Acetyl-$\gamma$-butyrolactone (20 gm) is dissolved in concentrated hydrochloric acid (60 ml). Decarboxylation sets in within a few minutes and
the reaction mixture becomes brown. After being allowed to stand for 10 hr at 25°, the solution is brought to pH 3-4 with sodium carbonate and extracted 5 times with ether (50 ml portions). The extracts are dried over Na₂SO₄, the ether evaporated, and the residue fractionated under vacuum, yielding 5-chloro-2-pentanone (11.9 gm, 63%) as a colorless liquid with a fruity odor, b.p. 57-60°/12 mm.

In 2N HCl at 20° or with warming (5). α-Acetyl-δ-caprolactone (4 gm) is suspended in 2 N HCl (16 ml) and the ice-cooled mixture stirred for 5 hr, during which time the carboxylic acid formed is partially decarboxylated. The 2,6-dimethyl-5,6-dihydro-4H-pyran-3-carboxylic acid which has precipitated is filtered and washed with ice-water. Yield 1 gm (25%); λ max 244 mμ, log ε 4.08 (λ max in 0.1 N NaOH, 236 mμ).

α-Acetyl-γ-butyrolactone (10 gm) is dissolved in 2N HCl (40 ml) and heated under reflux for 5 hr. The solution is brought to pH 5-6 with K₂CO₃ and extracted with ether. The ether is dried over Na₂SO₄ and evaporated and the residue fractionally distilled in vacuo, yielding 5-hydroxy-2-pentanone (72 gm, 90%) as a colorless oil, b.p. 98-101°/12 mm.

In methanol, followed by SOCl₂ (26). 2-Phenyl-4-hydroxyethylideneoxazolin-5-one (10 gm) is dissolved in methanol (100 ml) with gentle warming, and the excess methanol evaporated under vacuum. On cooling, the syrupy residue crystallizes as colorless cubes; these are powdered, recrystallized from petroleum ether (b.p. 60-90°), yielding colorless prismatic plates of α-benzoylaminoacetoacetic acid methyl ester (11.2 gm, 96.5%), m.p. 86-88°. These are dissolved in thionyl chloride (10 ml) and the solution warmed for several minutes until the evolution of gas subsides. Excess thionyl chloride is evaporated in vacuo and the residual crude 2-phenyl-5-methyloxazole-4-carboxylic acid methyl ester heated with 2 N sodium hydroxide (50 ml) until solution is complete; water (100 ml) is added and the mixture brought to the boil and filtered. On cooling, the filtrate is treated with 18% hydrochloric acid and the yellow precipitate filtered off. It is recrystallized from water (100 ml) containing a little ethanol and activated charcoal and dried in vacuo over CaCl₂, yielding colorless needles of 2-phenyl-5-methyloxazole-4-carboxylic acid (5.7 gm, 59%).

Preparation of the Dihydro Compounds

2-Methoxy-3-carbomethoxy-6-methyltetrahydropyran (20 gm) is treated with concentrated sulfuric acid (3 drops) and heated at 125-130° while dry nitrogen is bubbled through. The elimination of methanol is completed after approximately 1.5 hr. A little NaHCO₃ is added and the mixture fractionated under vacuum, yielding 3-carbomethoxy-6-methyl-
5,6-dihydro-4H-pyran (14.5 gm, 88%) as a colorless oil, b.p. 91°/11 mm (7).

2-Ethoxy-5,5-dimethyl-2,3-dicarbethoxytetrahydrofuran (5 gm) is treated with polyphosphoric acid (2 drops) and heated for 2 hr at 100° while dry nitrogen is bubbled through. The distillate is redistilled twice, yielding 5,5-dimethyl-2,3-dicarbethoxy-4,5-dihydrofuran (4.0 gm, 91%) as a colorless oil, b.p. 74°/0.1 mm, $\lambda_{\text{max}}$ 258 m$\mu$; log$e$ 3.94 (30).

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Besides the main maxima for the entire mesomeric system, the ethoxalyl and acetyl derivatives also exhibit smaller maxima in the short-wave range (205-210m$\mu$).


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$\alpha = \epsilon/M.W. = \log (I_\alpha/I) \times (1/c) \times (1/d)$ (c = concentration in grams per liter, d = thickness of layer).