4- AND 5-OXOCARBOXYLIC ACIDS AS VERSATILE SYNTHONS FOR THE PREPARATION OF HETEROCYCLES

Ferenc Csende\textsuperscript{a} and Géza Stájer\textsuperscript{b,*}
\textsuperscript{a}Taxus Pharmaceuticals, Vasvári P. u. 61, H-4440 Tiszavasvári, Hungary
\textsuperscript{b}Institute of Pharmaceutical Chemistry, University of Szeged, PO Box 121, H-6701 Szeged, Hungary, E-mail: stajer@pharma.szote.u-szeged.hu

Abstract – Conversions of 4- and 5-oxocarboxylic acids for the preparation of heterocycles are discussed. The review illustrates the importance and variability and presents the synthetic applicability of these versatile synthons.

CONTENTS
1. Introduction
2. Reactions with hydrazines
3. Reactions with hydroxylamine
4. Cyclocondensations with bifunctional amino derivatives
5. Cyclizations to lactones
6. Formation of lactams
7. Conversion to thiophene derivatives
8. Syntheses of natural products. Other ring systems

1. INTRODUCTION
In the course of our synthetic work, we have prepared numerous cycloalkane-condensed oxygen- and nitrogen-containing heterocycles and benzologues.\textsuperscript{1,2} New reactions of 4- and some 5-oxocarboxylic acids have been applied and some earlier results have been reinvestigated with special attention to the starting aroylcycloalkanecarboxylic acids. The present survey reports on the versatile applicability of these synthons, which, in spite of their extensive use, have not yet been reviewed.

Several methods are known for the synthesis of the starting oxocarboxylic acids. However, because of its simplicity and good to excellent yields, the Friedel-Crafts reaction has been the most widely applied.\textsuperscript{3-8} The numerous other methods described involve more steps or usually require special conditions. Besides the Friedel-Crafts preparation, the application of Grignard reactions has proved to be advantageous for variation of the aryl or alkyl substituents on the acyl group, this method resulting in few side-reactions.\textsuperscript{9-12}
The organolithium compounds are also useful in special cases.\textsuperscript{13-16} Other methods are based on the enamine reactions of cyclic ketones with piperidine or pyrrolidine, and then with a haloalkanoic ester,\textsuperscript{17} and the Reformatsky reaction of succinic anhydride with a bromoalkanoic ester.\textsuperscript{18} Condensation of anhydrides with malonic acid in the presence of triethylamine at 80 °C results in 2-acetylenbenzoic acids.\textsuperscript{19,20} When refluxed in toluene in the presence of piperidine, the aromatic aldehydes react with substituted levulinic acids to give arylidine-substituted oxocarboxylic acids.\textsuperscript{21} 2-(2-Pyridylcarbonyl)benzoic acid has been obtained by the thermal condensation of phthalic anhydride with 2-piperidinecarboxylic acid.\textsuperscript{22} The reaction of acrolein with nitroethane affords 4-nitropentanal; on subsequent treatment with aqueous hydrogen peroxide,\textsuperscript{23} 4-oxopentanoic acid is obtained. The reaction of 4-aroylecarboxylic acid with phthalic dicarboxaldehyde yields naphthaleneoxocarboxylic acid.\textsuperscript{24} In protic media, ethyl pyridazinecarboxylate undergoes reaction with aldehydes to furnish heterocyclic oxocarboxylic acids.\textsuperscript{25} When 2-iodocyclopentanecarboxylate is treated with zinc, and then with acid chlorides in the presence of palladium catalyst,\textsuperscript{26} aroylcyclopentanecarboxylic acids are prepared stereoselectively.

As numerous of the derivatives obtained from oxocarboxylic acids have significant pharmacological activity, these are also reported on in the present survey.

2. REACTIONS WITH HYDRAZINES

The reactions of aromatic 4-oxocarboxylic acids (4) (\textit{e.g.} phthalaldehydic acid) with hydrazines result in phthalazinones (5).\textsuperscript{45-55} (Scheme 2)
The 5-oxocarboxylic acids (6) undergo cyclization with hydrazine derivatives to afford 1,2-diazepinones (7) in low to good yields, with pyridone derivatives (8) as by-products.\textsuperscript{55-57} (Scheme 3)

The pyrolytic reactions of 2-acetylphenylacetic acid (10) with hydrazines yield 1-methyl-3\(H\)-2,3-benzodiazepin-4(5\(H\))-ones (11) in low yield, with 1-methyl-2-amino-3(2\(H\))-isoquinolinones as side-products.\textsuperscript{57} The analogous 1-aryl-2,3-benzodiazepine derivatives (e.g. 11) have noteworthy anxiolytic, anticonvulsant and neuroprotective activity.\textsuperscript{58,59} (Scheme 4)

In aqueous solution, the sulfuric acid-catalysed reaction of 3-methyl-4-oxopentanoic acid (12) with phenylhydrazine gives the indole derivative (13).\textsuperscript{60} (Scheme 5)
The phenylhydrazones of 14 have been cyclized to fused tetracyclic compounds containing an indole moiety (15). When R = COOEt, the carbazole (16) was formed. (Scheme 6)

On reaction with hexahydropyridazine, the mixed anhydride prepared from 3-p-methoxybenzoylpropionic acid (17) and ethyl chloroformate gives the hydrazides (18a) and (18b). Treatment with acid in toluene results in the unsaturated lactam (19) and then to 20 by catalytic hydrogenation, which on further reduction with LiAlH₄ yields the 1,6-diazacyclodecane (21). (Scheme 7)
The 1,2-diazetidin-3-one (26) is formed by reduction of the pyridazinone (23) with NaBH₃CN in acidic (2 N HCl) medium, followed by acylation–alkylation to 25 and 27, and cyclization by DCC or NaH.⁶³ (Scheme 8)

A similar procedure leads to lactams (30) (Scheme 9), which have the skeleton of peptide-type antibiotics, e.g. glidobactin A, isolated recently from a culture broth of *Polyangium brachysporum*.⁶⁴
The ring contractions of pyridazinone and phthalazinone derivatives with Zn/HCl to furnish pyrrolidines or isoindolines have been well studied.\textsuperscript{65-68} For the \textit{cis}- and \textit{trans}-cyclohexane-condensed pyridazinones (32), stereoselective ring contraction has been observed.\textsuperscript{69} (Scheme 10)

\begin{center}
\textbf{Scheme 10}
\end{center}

\textit{cis}, \textit{trans}; \textit{Ar} = C\textsubscript{6}H\textsubscript{4}Me-4 \hspace{1cm} \textit{cis}: (78\%), \textit{trans}: (70\%)

3. REACTIONS WITH HYDROXYLAMINE

Hydroxylamine reacts with oxo acids (34) to give 1,2-oxazines (35) by ring closure via an oxime intermediate.\textsuperscript{6,70-73} (Scheme 11)

\begin{center}
\textbf{Scheme 11}
\end{center}

The reactions of 3-aroylcyclopentanecarboxylic acid (36) esterified with diazomethane then with with hy-
droxylamine result in the oxime (37), which may be converted to the saturated 1,2-oxazepine (38) and the azabicyclo[3.2.1]octane (40).74 (Scheme 12)

The formation and further conversion of 2,3-benzoxazin-1-ones (42) to phthalimides (43), 3,1-benzoxazines (44) and phthalazines (45) has been described.75, 76 (Scheme 13)

On acid catalysis, the 2-acetylphenylacetic acid (46) reacts with hydroxylamine to afford the isoindole-carboxylic acid (48) instead of 1,2-oxazepinone.77 (Scheme 14)

4. CYCLOCONDENSATIONS WITH BIFUNCTIONAL AMINO DERIVATIVES

In spite of the acidity of the carboxyl group and the presence of strong intramolecular hydrogen-bonds, amino acids react with oxocarboxylic acids at higher temperature. The condensation of phthalaldehydic acid or 2-acetylbenzoic acid with anthranilic acid yields 5H-isooindolo[2,1-a][3,1]benzoxazine-5,11-dione (49).78 (Scheme 15) α-Amino acids (50) readily condense with 2-acetylbenzoic acid to afford the protected amino acid (51), with oxazole (52) as side-product.79 (Scheme 15) These 3- methyleneephthalidylamine acids (51) are simply cleaved with hydrazine to give the free amino acid and 1-methyl-4-phthalalzone.79
From phthalaldehydic acid (53) and 2-aminobicyclo[2.2.1]hept-5-ene-3-carboxylic acid (54), the 1,3-oxazino[2,3-a]isoindole-2,6-dione (56) (a new ring system) has been obtained in a retro Diels-Alder process.80 (Scheme 16) First the parent (55) is formed and its decomposition results in (56) by the loss of cyclopentadiene.

When the 4-oxo acids (57) are condensed with amino esters in the presence of isocyanides, the bicyclic lactams (59) may be prepared in a one-pot intramolecular Ugi reaction.81 (Scheme 17) By reacting 4- and 5-oxoalkanoic acids with anthranilic acid, anthranilamides or salicylamide, Aeberli and Houlihan obtained the heterocycles (60a,b).82
Phthalaldehydic acids (53) react with 2-aminobenzenesulfonamides to afford dihydro-11\(H\)-isoindolo[1,2-c][1,2,4]benzothiadiazin-11-one 5,5-dioxides (61).\(^{83, 84}\) (Scheme 18)

The condensations of oxo acids with 1,2-, 1,3-, or 1,4-amino alcohols or diamines or aminothiophenol result
in lactams (62a,b) condensed with an N-, O- or S-containing heteroring.\textsuperscript{82-88} Starting from ethyl levulinate (63), the rapid microwave irradiation in dry media yields the fused pyrrolidonones (64).\textsuperscript{89} (Scheme 19) The reactions of 2-aminoethylphenylarsin (66) with 4-oxopentanoic or 5-oxohexanoic acids (65), with acetic acid as catalyst, give 1-aza-4-arsabicyclo[3.3.0]octane or 1-aza-7-arsabicyclo[4.3.0]nonane (67) in good yields (65-80%).\textsuperscript{90} (Scheme 20)

![Chemical structure of 65 and 66 with reaction conditions and yields.]

Scheme 20

By the cyclocondensation of cis-2-p-methylbenzoyl-1-cyclohexanecarboxylic acid (68) with diaminoalkanes, aminoalkanols and aminothiols, saturated isoidole-condensed oxazole, 1,3-oxazine, pyrrolidine, piperidine, etc. have been prepared.\textsuperscript{91} On cyclization, a new chiral centre is formed and isomerization with ring opening occurs. (Scheme 21)

![Chemical structure of 68 with reaction conditions and yields.]

Scheme 21

It is noteworthy that the reaction of 68 with 2-aminoethanol in the presence of a catalytic amount of p-TSA results in octahydrooxazolo[2,3-a]isoindol-5(9bH)-one (69) exclusively. However, in toluene or xylene as solvent, the reaction leads to 70; with different acids, a catalysed rearrangement has been proved experimentally.\textsuperscript{92} With o-phenylenediamine, 68 gives the isoindolobenzimidazole (71), while the condensation with 2-aminothiophenol results in the thio analogue (72). Due to the acidic character of the hydroxy group, however, the reaction with o-aminophenol affords the lactam (73). (Scheme 22)
On application of aroylnorbornane- or aroylcyclohexane-carboxylic acid and stereoisomeric cycloalkane 1,3-diamines or aminoalcohols, heterocycles with five or more new chiral centres (74a, b) are formed; the stereoisomers has been isolated by column chromatography.\textsuperscript{109, 110}

The above polycyclic lactams have pharmacological activity: the 5-aryl-2,3-dihydro-5\textit{H}-imidazo[2.1-\textit{a}]isoindoles (75) prepared from tetrahydro-5\textit{H}-imidazo[2.1-\textit{a}]isoindol-5-one (62a) by reduction with LiAlH\textsubscript{4}\textsuperscript{111} (Scheme 23) exhibit an anorexic effect. The activity of 76 (Ar = 4-chlorophenyl) was found to be approximately equal to that of \textit{d}-amphetamine.

\begin{equation}
\text{Ar} - \text{COOH} \xrightarrow{\text{H}_2\text{NNNH}_2, \text{toluene, reflux, } 5\text{-}24 \text{ h}} \text{Ar} - \text{N}\text{NH}
\end{equation}

\begin{equation}
\text{Ar} \xrightarrow{\text{LiAlH}_4, \text{THF, } < 30 \text{ °C, } 6 \text{ h}} \text{Ar} \text{OH}
\end{equation}

\begin{align}
A/B & \quad Q & n & \text{yield (%)} & \text{ref.} \\
\text{cis} & (\text{CH}_2)_2 & 2 & 52 & 120 \\
\text{trans} & \text{CH}=\text{CH} & 2 & 67 & 105 \\
\text{cis} & \text{CH}=\text{CH} & 1 & 46 & 120
\end{align}

Scheme 22

\begin{align}
\text{Ar} & \quad \text{yield (%)} \\
\text{Ph} & \quad 21 \\
\text{2-thienyl} & \quad 15 \\
\text{2-pyridyl} & \quad 30 \\
\text{C}_6\text{H}_4\text{Cl-4} & \quad 65
\end{align}

Scheme 23
A series of bicyclic analogues of succinimide and glutarimide have been synthesized by reaction of the oxo carboxylic acid with diamines and evaluated for CNS activity.\textsuperscript{112} The tetrahydropyrrolothiazolone (77a) and \textsuperscript{[2,1-b]}benzothiazolone (77b) have anticonvulsant activity.\textsuperscript{113} (Scheme 24) Some other tetrahydro-1\textit{H}-pyrrolo[1,2-\textit{a}]benzimidazol-1-one derivatives have been found to be effective in sound- and electroshock-induced seizures.\textsuperscript{114} Other derivatives, \textit{e.g.} 78 (R\textsubscript{1},R\textsubscript{2},R\textsubscript{3} = H, Cl, OMe, NO\textsubscript{2}) exert cytotoxic activity on mammalian cell lines and myeloma, ovarian and colon cancer lines.\textsuperscript{115, 116} The substituted 2,3-dihydrothiazolo[2,3-\textit{a}]isoindolone, \textit{e.g.} the R\textsubscript{–}(+) isomer of 79 inhibits the reverse transcriptase of human immune deficiency virus 1 (HIV-1)\textsuperscript{117} and replicates the HIV-1 in MT2 cells.

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) \textbf{77a};
\node (b) at (1,0) \textbf{77b};
\node (c) at (2,0) \textbf{77b};
\node (d) at (3,0) \textbf{78};
\node (e) at (4,0) \textbf{79};
\end{tikzpicture}
\end{center}

\textbf{Scheme 24}

From aminodiol or hydroxyalkylenamine with oxoacids, tetrahydropyrrolo[2,1-\textit{b}]oxazol-5(6\textit{H})-ones (80a,b) and oxazine homologues (81a,b) have been prepared (Scheme 25); one derivative was found to display marked hypoglycaemic activity \textit{in vivo}.\textsuperscript{118}

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) \textbf{80a} (11%); \node (b) at (1,0) \textbf{80b} (23%);
\node (c) at (2,0) \textbf{81a} (41%); \node (d) at (3,0) \textbf{81b} (37%);
\node (e) at (0,-2) \textbf{80a} (11%); \node (f) at (1,-2) \textbf{80b} (23%);
\node (g) at (2,-2) \textbf{81a} (41%); \node (h) at (3,-2) \textbf{81b} (37%);
\end{tikzpicture}
\end{center}

\textbf{Scheme 25}
From the reactions of 2-ethoxycarbonylmethyl-1-cycloalkanones (82) with \(\alpha,\omega\)-diaminoalkanes, the tricyclic lactams (83) have been prepared.\textsuperscript{119} (Scheme 26) The similar reaction with alicyclic 1,3-aminoalcohols result in tetra- and pentacyclic lactams, e.g. the pyrrolo[1,2-\(\alpha\)][3,1]benzoxazines.\textsuperscript{120-122}

![Scheme 26]

Treatment of the isoindolo[1,2-\(b\)]benzothiazol-10(5\(a\)H)-one S-oxide (86) with \(p\)-TSA in toluene results in the thiazine (87) by oxidative ring expansion. As a mechanism, the formation of a sulfenic acid intermediate was supposed. The new isoindolo[1,2-\(c\)][1,4]benzothiazin-11-one (88) was also formed.\textsuperscript{20} (Scheme 27)

![Scheme 27]

The tetracyclic thiolactams (93) have been prepared in several steps.\textsuperscript{123} The oxo acids (89) were nitrated, and then esterified and treated with ethylenediamine to furnish the intermediate (91) in a multistep one-pot reaction. Reduction and subsequent thiourea ring formation proceed through 92 to result in the hexahydro-imidazo[4,5,1-\(j,k\)]pyrrolo[1,2-\(d\)][1,4]benzodiazepine-10(11\(H\))-thiones (93). (Scheme 28) These compounds significantly inhibit HIV-1 replication \textit{in vitro}. 

<table>
<thead>
<tr>
<th>m</th>
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<th>yield (%)</th>
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<tr>
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<td>41</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>29</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>32</td>
</tr>
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</table>
Synthesis of the diazasteroid-like 96 was achieved by the condensation of levulinic ester (94) with aminoethylisoquinoline (95). (Scheme 29)

For the preparation of 1H-phthalazino[1,2-b]quinazolin-8-ones, other multifunctional amines, e.g. anthranilic hydrazide, have been applied. The reaction has been extended to aminocyclohexanecarboxyhydrazides, furnishing regio- and stereoisomers (98) and (99). (Scheme 30)
5. CYCLIZATIONS TO LACTONES

For 4- and 5-oxocarboxylic acids, the ring-chain tautomeric interconversion proceeding via intramolecular reversible addition to the C=O group has been well studied.130-132 (Scheme 31)

The dehydration of levulinic acid (22) by means of strong acids or acetic anhydride results in 2(5H)-furanone (101) and 2(3H)-furanone (102), with different positions of the C=C bond.133-137 (Scheme 32)

Miyano et al. isolated four diastereoisomeric 3-phenylhexahydro-1(3H)-isobenzofuranones (103-106).138
Scheme 33

Stereoisomeric 3-methylhexahydrophthalides\textsuperscript{139} and similar lactones have been prepared by reduction with metal hydrides or \( \text{H}_2/\text{PtO}_2 \) catalyst\textsuperscript{140}. Clemmensen reduction of 2-aroylbenzoic acids gave 3-phenylphthalides in good yield\textsuperscript{141}. Another route to lactones is the asymmetric reduction with bakers' yeast (\textit{Saccharomyces cerevisiae}), with >98\% ee\textsuperscript{142-147} (Scheme 34) The optically active lactones (109) are key intermediates in the synthesis of natural products.

Scheme 34

The Reformatsky reaction and spontaneous cyclization of 94 result in lactone 111\textsuperscript{148} (Scheme 35)
The pyrolysis of 1-ethoxypropenyl esters of 2-formyl and 2-acylbenzoic acids (112) affords ethyl α-(1-substituted-1-phthalidyl)propionates (113) in high yields.\textsuperscript{149} 113 can also be prepared by the Reformatsky reaction of ethyl α-bromopropionate with ethyl 2-acylbenzoates, but with low yields. (Scheme 36)

Further methods are known for the formation of lactones, e.g. the acid-catalysed condensations of phthalaldehydic acid or 2-acetylbenzoic acid with benzene and naphthalene derivatives yield 3-phenyl- and 3-(1-naphthyl)phthalides.\textsuperscript{19, 150, 151} (Scheme 37)

The condensation of 2-(4-fluorobenzoyl)benzoic acid with \textit{m}-cresol in the presence of anhydrous ZnCl\textsubscript{2} at
115-120 °C for 8 h furnishes two isomeric products (116a) and (116b) in different ratios.\textsuperscript{152,153} (Scheme 38) 116a can be converted to dibenzo[b,e]oxepinone (118) via 117, which is obtained by the reduction of 116a with zinc–acetic acid.\textsuperscript{154}

The hydroxymethylation of 3-aroylpropionic acids leads to 4-aroyl-2(3H)-dihydrofuranones (120), which are in a pH-dependent equilibrium with the open form (119).\textsuperscript{155} (Scheme 39)

\[
\begin{align*}
\text{COOH} & \xrightarrow{\text{HCHO}} \text{COONa} \xrightarrow{\text{H}^+} \text{O} \quad \text{Ar} \\
17 & \xrightarrow{\text{NaOH}} \text{HO} \quad \text{Ar} \xrightarrow{\text{OH}^-} \text{O} \quad \text{Ar} \\
119 & \xrightarrow{\text{COOH} \quad \text{Ar}} \text{120} \\
\end{align*}
\]

Scheme 39

Hypervalent iodine oxidation with hydroxy(tosyloxy)iodobenzene yields aroyl-γ-lactones.\textsuperscript{156} In the case of 4-benzoylbutyric acid (121), 5-benzoyldihydro-2(3H)-furanone (122) was obtained. From the oxo acid (123), by oxidative cyclization, the tricyclic ring system (124) was formed stereoselectively in good yield (78%). (Scheme 40)

\[
\begin{align*}
\text{C}_6\text{H}_4\text{I(OH)}\text{OTs} & \xrightarrow{\text{CH}_2\text{Cl}_2, 15 \text{ h}} \text{Ph} \\
121 & \xrightarrow{\text{Ph}} 122 (74\%) \\
\text{MeO} \quad \text{COOH} & \xrightarrow{\text{C}_6\text{H}_4\text{I(OH)}\text{OTs}} \text{MeO} \\
123 & \xrightarrow{\text{MeO}} 124 (78\%) \\
\end{align*}
\]

Scheme 40

The readily enolizable 3-benzoylpropionic acid (17) has been cyclized with triphenylphosphine to enol lactones (125) and (126), in 75% yield. (Scheme 41)\textsuperscript{157}

\[
\begin{align*}
\text{O} & \xrightarrow{\text{P(Ph)}_3, \text{CH}_2\text{Cl}_2, \text{CCl}_4} \text{Ph} \\
125 (75\%) & \xrightarrow{\text{Ph}} \text{O} \\
\text{COOH} & \xrightarrow{\text{P(Ph)}_3, \text{Et}_3\text{N}, \text{CH}_2\text{Cl}_2, \text{CCl}_4} \text{Ph} \\
17 & \xrightarrow{\text{(Ph)}_3\text{P}} 126 (20\%) \\
\end{align*}
\]

Scheme 41
Treatment of 2-acyl-3-nitrobenzoic acid (127a,b) with Ac₂O in the presence of sodium acetate results in nitrophthalide (128) on fusion, or 129 on reaction with substituted benzene and conc. sulfuric acid.¹⁵⁸ (Scheme 42)

\[
\begin{align*}
\text{COOH} & \quad \text{O} \\
\text{NO}_2 & \quad \text{R}^1 \\
& \quad \text{127a} \\
\text{O} & \quad \text{OH} \\
\text{NO}_2 & \quad \text{R}^1 \\
& \quad \text{127b} \\
\text{Ac}_2\text{O}, \text{AcONa} & \\
\text{fusion} & \\
\text{Ph}–\text{R}^2 & \quad \text{conc. H}_2\text{SO}_4 \\
\end{align*}
\]

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<th>R(^1)</th>
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<th>R(^2)</th>
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<tbody>
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<td>Ph</td>
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</tr>
<tr>
<td>C(_6)H(_5)Me-4</td>
<td>4-OH</td>
<td>70</td>
</tr>
<tr>
<td>H</td>
<td>4-OH</td>
<td>79</td>
</tr>
</tbody>
</table>

Scheme 42

Chlorination of levulinic acid (22), followed by triethylamine treatment, promotes the elimination of HCl to lead to the formation of 5-(chloromethyl)hydroxyfuranones (132) and (134).¹⁵⁹ (Scheme 43)

\[
\begin{align*}
\text{COOH} & \quad \text{Cl} \\
\text{CH}_2\text{Cl} & \\
& \quad \text{130} \\
\text{Et}_3\text{N}, \text{CH}_2\text{Cl}_2 & \\
3 \text{h} & \\
\end{align*}
\]

ratio 4:1 (50-70%)

\[
\begin{align*}
\text{COOH} & \quad \text{Cl} \\
\text{CH}_2\text{Cl} & \\
& \quad \text{133 (96%)} \\
\text{SO}_2\text{Cl}_2 & \\
\text{UV, 1 h} & \\
\end{align*}
\]

\[
\begin{align*}
\text{COOH} & \quad \text{Cl} \\
\text{Me} & \\
& \quad \text{22} \\
\text{Cl} & \quad \text{COOH} \\
\text{CH}_2\text{Cl} & \\
& \quad \text{134 (5%)} \\
\text{Et}_3\text{N}, \text{CH}_2\text{Cl}_2 & \\
24 \text{h} & \\
\end{align*}
\]

Scheme 43
The Friedel-Crafts reaction of cis-tetrahydrophthalic anhydride with toluene at –10 °C proceeds via the oxocarboxylic acid to afford the 2-(4-methylphenyl)-6-oxabicyclo[3.2.1]octan-7-one (135). In the presence of more (1:2) AlCl₃, the reaction yields the 7-(4-methylphenyl)-6,10-dioxatricyclo[5.2.1.0¹⁸]decan-5-one (136). With diendo-5-norbornene-2,3-dicarboxylic anhydride as starting material, the methylene-bridged analogues (137) and (138) are obtained. (Scheme 44)

![Scheme 44](image)

When camphoracetic acid (139) is reacted with NaBH₄, and then with sulfuric acid, the endo-fused lactone

![Scheme 45](image)
(140) is obtained. (Scheme 45) Treatment with thionyl chloride yields the chloro compound (142). Subsequent reduction with tributyltin hydride and DIBALH, through 140, results in the lactol (141), which is a useful reagent in racemate resolution and asymmetric syntheses.162

6. FORMATION OF LACTAMS

The 4- and 5-oxocarboxylic acids (143) or their esters react facilely with amines to give γ- or δ-lactams. In the Leuckart reaction with formamide at 180 °C, the oxo acids give 2-pyrrolidones or 2-piperidinones (144).163 (Scheme 46)

\[
\begin{align*}
\text{R} \text{O} \text{COOH} \quad \xrightarrow{\text{CONH}_2} \quad \text{R} \text{NH}_2 \text{COOH}
\end{align*}
\]

R = H, Me, Ar; n = 1, 2

Scheme 46

The cis- and trans-2-aroylcyclohexanecarboxylic acids (68) condense with primary amines under mild conditions, while the aryl- or hetarylamines react only under forceful conditions (e.g. fusion), to result in hexahydroisoindolones (145).69 (Scheme 47)

\[
\begin{align*}
\text{Ar} = \text{C}_6\text{H}_4\text{Me}-4
\end{align*}
\]

Scheme 47

A one-step conversion of 2-acylbenzoic acids to 3-oxodihydroisoindoles has been developed, involving reductive amination with sodium cyanoborohydride or sodium borohydride in acetonitrile.164 Another modified method of reductive amination with sodium triacetoxyborohydride and primary amines has also
been described. Highly enantioselective preparations of 6-alkylpiperidin-2-one derivatives (148a,b) and (149a,b) have been achieved by using 2-amino alcohols as chiral auxiliaries. In the first step, bicyclic lactams (147a,b) are formed, which are then opened with reducing agents (Scheme 48).

![Scheme 48]

The synthesis of an azasteroid from estrone has been achieved. The 11-aza-C-homoestrane (151) was prepared from the oxo acid (150) by treatment with thionyl chloride and ammonia, and subsequent acid-catalysed cyclization. (Scheme 49)

![Scheme 49]

The condensations of oxocarboxylic acids (1) or (6) with 2-phenylethylamines, tryptophane or tryptamine to furnish isoquinoline or β-carboline derivatives 153 have been reported. (Scheme 50)
On application of the Pictet-Spengler reaction in aprotic media, tetracyclic lactams were obtained in good yields (80%) from oxoglutaric acid.\textsuperscript{176} The treatment of 3-hydroxyphenylethylamine with oxoacids in the presence of solvent and an acidic catalyst, or by fusion at 150-200 °C, results in the hexahydropyrrolo[2,1-\textit{a}]isoquinolin-3-ones (154) and benzo[\textit{a}]quinolizinones.\textsuperscript{177, 178} (Scheme 51)

In the reaction with thienylethylamine, an intramolecular amidoalkylation by acidic catalysis \textit{via} the \(\alpha\)-hydroxylactam (157) was initially presumed.\textsuperscript{179} (Scheme 52) The intermediate (157) forms an acyliminium ion by water elimination and this, on cationic cyclization, yields the tricyclic lactam (158).\textsuperscript{179-182}
The synthesis of hexahydro-3-oxo-1H-indolizino[8,7-b]indoles (162) from tryptamine-2-carboxylic acids (159), based on the carboxyl-mediated Pictet-Spengler reaction, has been described.\(^\text{183}\) (Scheme 53)

Another route could be the condensation of an oxo acid to the phenylphthalimidine (163), followed by transformation by phase-transfer alkylation with 1-bromo-3-chloropropane to the tricyclic lactam.\(^\text{184}\) (Scheme 54) 164 and its pyrido analogues display virucidal activity.
A simple synthesis of *N*-substituted lactams (165) is the condensation of oxo acid with alkylamines in the presence of isocyanides at room temperature.185 (Scheme 55)

Isocyanides have also been used for preparations from 2-formyl- or 2-acylbenzoates with the application of isocyanatoacetates and sodium hydride in DMF; by means of this route, the one-step synthesis of 1-oxo-1,2-dihydroisoquinoline derivatives (166) has been achieved.186 (Scheme 56)

3,4-Diarylisoquinolones (168) have been prepared by treatment of 2-aroylbenzoic acid with thionyl chloride, and then with benzylamine; the lactams (167) obtained are converted through ring opening with LDA to isoquinolines.187 (Scheme 57)
A facile and highly stereoselective formation of the polycyclic isoindolinones (170a,b) has been attained with strong Lewis acids (e.g. SnCl₄, TiCl₄, BF₃·OEt₂ and TMSOTf) by N-acyliminium ion cyclization. (Scheme 58)
7. CONVERSION TO THIOPHENE DERIVATIVES

The AlCl₃-catalysed Friedel-Crafts acylation of thiophene with naphthalene dicarboxylic anhydride in 1,2-dichloroethane affords the oxo acid (171) in good yield; this can then be reduced and cyclized to a thiophene analogue of tetralone, anthrone or naphthacenone (173).₁₈⁹-₁₉² (Scheme 59)

![Scheme 59](image)

Oxocarboxylic acids can be converted to thiophene derivatives with the Lawesson’s reagent in toluene;¹⁹³, ¹⁹⁴ depending on the molar ratio, 175 or 176 is formed. (Scheme 60)

![Scheme 60](image)

8. SYNTHESES OF NATURAL PRODUCTS. OTHER RING SYSTEMS

Certain parts of the total synthesis of alkaloids have been performed from cyclic 4-oxocarboxylic acids,
e.g. in the preparation of *Erythrina* alkaloids by the cyclization of 2-phenylethylamines with ethoxycarbonylmethylcyclohexanone (82).\(^{195,196}\) (Scheme 61)

The cytotoxic quinonone (183) has been synthesized from furan and phthalic anhydride,\(^{197}\) and also isolated from the stem bark of *Tabebina cassindes*. (Scheme 62)

Montaine-type *Amaryllidaceae* alkaloids, which possess a 5,11-methanomorphanthridine ring system e.g. 190, have been prepared stereoselectively from aroylcyclohexene carboxylic acids (184).\(^{198,199}\) (Scheme 63)
The formal synthesis of strychnine started from the 2-oxoglutaric acid ester (191) and tryptamine. After reduction and ring expansion of 192, the tricyclic 193 containing a nine-membered ring was obtained, which is a key intermediate for the preparation of strychnine. (Scheme 64)

![Scheme 64](image)

From oxocarboxylic acids, special ring systems involving both small and large heterocyclic rings can be prepared. Thus, the synthesis of 4-benzoyl-2-azetidinones (197) starts from 3-benzoylpropionic acid (17); by bromination and condensation with anilines, 196 is obtained. Cyclization with a base (Et₃N, NaOMe, n-BuLi or Amberlite IRA-400), furnishes the azetidinones (197) in poor to good yield. (Scheme 65)

![Scheme 65](image)

<table>
<thead>
<tr>
<th>Ar</th>
<th>conditions</th>
<th>temp. (°C)</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>NaOMe EtOH</td>
<td>22</td>
<td>35</td>
</tr>
<tr>
<td>H</td>
<td>n-BuLi THF</td>
<td>-30</td>
<td>28</td>
</tr>
<tr>
<td>C₆H₄Me-4</td>
<td>IRA-400 EtOH</td>
<td>22</td>
<td>60</td>
</tr>
<tr>
<td>C₆H₄Cl-4</td>
<td>IRA-400 EtOH</td>
<td>22</td>
<td>28</td>
</tr>
</tbody>
</table>

Scheme 65
From 17, the phenylphthalide (109) is obtained by reduction (see Section 5); its condensation with substituted phenols results in benzoxepinones (198).202 (Scheme 66)

![Scheme 66](image)

On reaction with anilines, 2,3-dihydro-1H-benzazepin-2-ones (200) are obtained;203 their structures have been proved.204 (Scheme 67)

![Scheme 67](image)

From 2-benzoylbenzoic acid, 2,4-benzodiazepin-1-ones (204) are synthesized and then oxidized to 205.205 (Scheme 68)

![Scheme 68](image)
The formation of condensed systems containing an eight-membered ring is another field of application of 4-oxocarboxylic acids. Imidazo[2,1-\(a\)]isoindol-5-ones (62a) (see Section 4) have been prepared by the reactions of 2-arylbenzoic acids with ethylenediamine; on reduction with LiAlH\(_4\) in dry ether, this affords the hexahydro-2,5-benzodiazocines (206); the isomers may be resolved with \(d\)-camphorsulfonic acid.\(^{206}\) (Scheme 69)

3,4,5,6-Tetrahydro-5-methyl-1-phenyl-1\(H\)-2,5-benoxazocine (207) (Nefopam\(^{®}\)) has excellent analgetic and muscle relaxant activity. Several alternative methods have been developed for its preparation;\(^{207,208}\) one of them starts from 41. (Scheme 70)

On reaction of dihydroisoindolylalkanol precursors with cyanogen bromide via ring enlargement, a modified preparation of Nefopam and a homologue has been devised.\(^{210}\) The fully saturated derivatives have been prepared from 31 in a number of steps.\(^{211}\) (Scheme 71)
The synthesis of two macrocyclic rings illustrates the versatility of the 4-oxocarboxylic acid synthons; the tricycle 215 containing a ten-membered ring has been prepared by dimerization of the lactam (62b) in protic media. (Scheme 72) The structure was confirmed by X-Ray analysis.212

Scheme 71

The synthesis of two macrocyclic rings illustrates the versatility of the 4-oxocarboxylic acid synthons; the tricycle 215 containing a ten-membered ring has been prepared by dimerization of the lactam (62b) in protic media. (Scheme 72) The structure was confirmed by X-Ray analysis.212

Scheme 72

From 2-acetylbenzoic acid (4), a simple and template synthesis of zinc tetrabenzo[h,g,l,q]porphine (216) has been achieved in one step.213 (Scheme 73)
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