9.02 Oxepanes and Oxepines

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9.02.1 INTRODUCTION

This chapter follows on from the review by Boyd in the first edition of Comprehensive Heterocyclic Chemistry (CHEC-I), which dealt with oxepanes and oxepines <84CHEC-I(7)547>. The literature published from 1982 until 1993 (taken from Chemical Abstracts) is reviewed, as well as citations from some important earlier publications. This chapter does not contain a section devoted to...
reactivity of substituents. Data of this kind are considered in Sections 9.02.5–9.02.9, since they are of little importance in the sections associated with other reactions and syntheses of oxepines and oxepanes. Syntheses of \(\varepsilon\)-caprolactone are omitted, its reactivity is included only to demonstrate transformations leading to other oxepanes and hydrooxepines.

9.02.2 THEORETICAL METHODS

Several quantum chemical calculations using both semiempirical and \textit{ab initio} methods concerning the oxepin (1), benzene oxide (2), and their equilibrium should be noted (Equation (1)) \cite{83MI902-01, 84MI902-01, 90MI902-01}. The fully optimized geometry data \cite{90MI902-01} agree with experimentally found geometry of several substituted oxepines (see Section 9.02.3). Accordingly to calculations, the carbon skeleton of benzene oxide is practically planar while the angle between the epoxide ring and adjacent plane is ca. 106°; whereas the oxepin molecule is boat-shaped with folding angles along the two lines between \(C_2—C_7\) (1) and \(C_3—C_6\) ca. 137 and 159°, respectively.

\begin{equation}
\text{(1)}
\end{equation}

Semiempirical (AM1) and \textit{ab initio} (6-31G) calculations of naphthalene oxides (3)–(5) show that the benzene nucleus retains benzenoid character while in both benzene oxide and oxepin a polyenic nature is found \cite{91MI902-01}. Molecular mechanics calculations were used in conformational studies of some complicated oxepanes, i.e. 3,3,6,6-tetramethyloxepan-4,5-dione \cite{83JCS(P2)1351} and a 14β-steroid possessing an oxepan ring as a 17β-substituent \cite{86ZN(C)297}.

9.02.3 EXPERIMENTAL STRUCTURAL METHODS

The first x-ray crystal structure analysis data for a monocyclic oxepin appeared in 1982 when the structure of 3,7-di-\(t\)-butyl-5-phenyl-2-(\(p\)-tolyloxepin was published \cite{82CB385}. The data shows that the substituted oxepin exists in a boat conformation with dihedral angles between \(C_2OC_7\) and \(C_2C_6C_7C_8\) planes 117.6°, and that between \(C_2C_4C_7C_8\) and \(C_3C_4C_5C_6\) planes 150.7° (cf. the above data from quantum chemical calculations for the unsubstituted oxepin). Double and single bonds in the molecule show some degree of equalizing: \(O—C_2\) 1.424, \(C_2—C_3\) 1.393, \(C_3—C_5\) 1.426, \(C_5—C_6\) 1.367, \(C_5—C_6\) 1.441, \(C_6—C_7\) 1.323, and \(C_7—O\) 1.404 Å. Similar geometry has also been demonstrated for 2,7-diphenyloxepin \cite{86JOC2784} and 7-\(\beta\)-butoxycarbonyloxepin \cite{86CC970}. The x-ray data for fused dibenzoepxin is also available \cite{82AX(B)200}.

Low-temperature NMR studies of 2-cyano- and 2-ethoxycarbonyl-7-ethyloxepines provided evidence for a nonplanar geometry with a ring inversion barrier of 6.5 kcal mol\(^{-1}\) besides rotational isomerism involving 2-ethoxycarbonyl substituent \cite{86CC970}. The geminal methylene protons in \(\alpha\)-benzoyloxytoluene-2,3-oxide appeared as a singlet at ambient temperature and split into an AB system at \(-135\)°C, which supports the existence of two enantiomers, also in the equilibrium (Scheme 1) ca. 5% of the oxepin isomer was present \cite{88T7551}. Analogous equilibrium was shown in the case of 3-ethynaphthalene-1,2-oxide \cite{88T7551}. The \(^{13}\)C NMR spectra of partially hydrogenated oxepines, namely 2,3,4,5-tetrahydroxepin \cite{85JOC5583} as well as its anions and 2,3-dihydroxepin \cite{82JOC3094} were investigated.

\begin{equation}
\text{(2)}
\end{equation}

\begin{equation}
\text{(3)}
\end{equation}

\begin{equation}
\text{(4)}
\end{equation}

\begin{equation}
\text{(5)}
\end{equation}

\textbf{Scheme 1}
9.02.4 THERMODYNAMIC ASPECTS

Thermodynamic parameters of oxepines and oxepanes are considered, calculated, or measured in many publications. Among them, those which dealt with enthalpies of formation of oxepan and oxepin (92MI 902-01) and energetics of the arene oxide–oxepine valence isomerization (83JCS(P2)1351, 83MI 902-01, 84JA7696, 87T7551, 90MI 902-01, 91MI 902-01) are cited. The MNDO calculations (83MI 902-01) show that, in the gas phase, oxepin is more stable than benzene oxide, while in polar media the inverse is true. Dynamic NMR study (88T7551) gave the following activation parameters for the valence isomerization/degenerate racemization process: ΔG* = 7.6 kcal mol⁻¹, ΔH* = 8.6 kcal mol⁻¹, and ΔS* = 5.8 eu.

A dynamic NMR study (83JCS(P2)1351) of a saturated compound, 3,3,6,6-tetramethyloxepan-4,5-dione, gave evidence for two conformations, a distorted chair and a twist-boat, the latter being less favorable (by 1.91 kcal mol⁻¹). Both conformations have similar CO—CO dihedral angles, 87.2 and 88.6°, respectively. An inversion barrier as high as 8.6 kcal mol⁻¹ (at 171K in CHCl₃/F) was obtained.

Oxepin and benzo[c]oxepin as well as numerous other unsaturated cyclic systems were treated in terms of the concept of absolute and relative hardness (HOMO–LUMO gap) as a measure of aromaticity (89JA7371). Both of these systems were shown to be nonaromatic; however, it should be noted that, according to (89JA7371), the latter belongs to the same category as such O-heterocyclic systems, for example furan.

9.02.5 REACTIVITY OF FULLY CONJUGATED RINGS

The survey of reactivity of oxepines given in CHEC-I (84CHEC-I(7)547) is still noteworthy. The survey in CHEC-I covers such topics as (i) thermal and photochemical reactions, (ii) electrophilic attack on the ring oxygen atom, (iii) nucleophilic attack on carbon atoms, and (iv) reactions involving cyclic transition states. Considering other reactions of oxepines, the existence of oxepin–arene oxide equilibrium should be taken into account since some of the reactions can involve the latter form. Specific properties of the arene oxide system make it possible to interpret why electrophilic attack at carbon, and nucleophilic attack at the hydrogen atom, are not characteristic of oxepines. There is a lack of information devoted to reactions of oxepines with, for example, radicals and carbenes.

Considered below are two groups of oxepin reactions: (i) addition and cycloaddition reactions peculiar to their conjugated carbon chain, and (ii) those characteristic of vinyl ethers, particularly, beginning from an attack on ring oxygen. Both reaction types have been discussed in detail in CHEC-I; thus, only several important new examples are given here.

9.02.5.1 Addition and Cycloaddition Reactions

Successive addition of bromine to oxepin and the action of cyclopentadienylmagnesium bromide, followed by the treatment with triethylamine was used for the synthesis (albeit in a low yield) of a higher vinylogous fulvalene (6) (Scheme 2) (84CB2006).

\[ \begin{align*}
\text{Oxepine} & \quad \text{Br}_2 \quad \text{Br} \quad \text{C}_6\text{H}_5\text{MgBr} \quad \text{Br} \\
& \quad \text{Br} \quad \text{Br} \quad \text{O} \quad \text{Br} \\
& \quad \text{Br} \quad \text{Br} \quad \text{O} \quad \text{Br}
\end{align*} \]

(6) Scheme 2
A study of Diels–Alder reactions of three oxepines differing in the positions of oxepin–benzene oxide equilibria, namely unsubstituted oxepin (considerable amounts of both valence isomers), 2,7-dimethyloxepin (principally in the oxepin form), and indene oxide (predominantly benzene oxide form), has shown that all three compounds act exclusively in [4 + 2] cycloaddition reactions as benzene oxides, giving endo-adducts with anti-configuration relative to the bridge oxygen atom \( \langle 91 \text{JC1337} \rangle \).

An interesting and important reaction of oxepines is their participation as dienophiles in [2 + 4] cycloaddition with inverse electron demand. Using 1,2,4,5-tetrazines or 1,2,4-triazines bearing electron-withdrawing substituents as dienes, this reaction leads to dihydrooxepino[4,5-d]pyridazines (7) or dihydrooxepino[4,5-c]pyridines (8), each of which can be oxidized to corresponding oxepino[4,5-d]pyridazines (9) or oxepino[4,5-c]pyridines (10); the latter are converted by the treatment with an acid to cyclopenta[d]pyridazines (11) or cyclopenta[c]pyridines (12), respectively (Scheme 3) \( \langle 83 \text{CB97} \rangle \).

In the case of unsubstituted oxepin, the [2 + 4] cycloaddition competes with [4 + 6] process giving, for example a phthalazine derivative (13) besides (7) in the ratio (7): (13) = 2:1. 2,7-Dimethyloxepin probably cannot undergo the [4 + 6] cycloaddition reaction owing to steric hindrances in its first step, i.e. the formation of an intermediate like (14) (Scheme 4).

9.02.5.2 Cleavage of the Oxepin Ring

Some of the processes considered above involve the cleavage of the oxepin ring, for example acid-catalyzed hydrolytic scission of one of the C—O bonds, followed by the formation of five-membered
carbocycles ((9)→(11) and (10)→(12)) or rearrangement of the intermediate 1,6-oxido-3,4-
diaza[3,4]annulene (15), followed by dehydration of the formed 1,4-dicarbomethoxy-4a-hydroxy-
4a,8a-dihydrophthalazine (16), which gives the phthalazine derivative (13) \( <83CB97> \). However, only
the former can be regarded as a true transformation of fully conjugated oxepin; while the latter
takes place in the dihydrooxepin system. Another possibility in the cleavage of the oxepin ring is its
opening by oxidation reactions. For example, it was shown (Equation (2)) \( <89JCS(P1)133> \) that the
photooxidation of oxepino[2,3-b]benzofuran derivative (17) in \( \text{Me}_2\text{CO—MeOH} \) mixture containing
tetraphenylporphin leads to the formation of the benzofuranone (18).

![Chemical structure](image)

\[ \begin{align*}
\text{MeO} & \quad \text{Bu}^1 \\
\text{MeO} & \quad \text{COBu}^1 \\
\text{MeO} & \quad \text{MeOH} \\
\end{align*} \]

\[ \text{MeO} \quad \text{Bu}^1 \]

(2)

9.02.6 REACTIVITY OF NONCONJUGATED RINGS

In CHEC-I \( <84CHEC-I(7)547> \), the reactivity of oxepanes was discussed in the following subsections:
(i) thermal and photochemical reactions, (ii) electrophilic attack on the ring oxygen atom, (iii)
nucleophilic attack on carbon atoms, (iv) reactions with radicals or electron-deficient species, and (v)
oxidations, reductions, and reactions involving cyclic transition states. These subsections
practically cover all types of reactivity of oxepanes as saturated cyclic ethers. However, data
cconcerning partially saturated oxepines was not considered in CHEC-I and this is done here. Some
reactions of highly unsaturated compounds with conjugated systems which, in contrast to oxepines,
cannot be even formally regarded as closed ones, namely oxepinones, oxepindiones, oxepin oxides,
are also considered.

9.02.6.1 Dihydrooxepines

Reactions of polyunsaturated compounds, which can be formally related to dihydrooxepines,
 i.e. oxepinones, oxepindiones, and oxepin oxides, are noteworthy. The addition reactions of \( N \-
nucleophiles to both benzene oxide and symmetrical oxepin oxide were studied as models for the
biogenesis of some natural epidithiadioxopiperazines of gliotoxin and aranotoxin families (Equation
(3)) \( <82JOC1509> \).

![Chemical structure](image)

\[ \begin{align*}
\text{O} & \quad \text{N} \\
\text{O} & \quad \text{OH} \\
\end{align*} \]

(3)

Chemical behavior of oxepin-2,7-diones is, in general, normal of anhydrides of double unsaturated
conjugated carboxylic acids. Thus, methanolysis of 4-methyloxepin-2,7-dione leads to a mixture of
isomeric monomethyl (2Z,4Z)-3-methyl-2,4-hexadienedioates \( <82JOC1212> \). 3,6-Dimethyloxepin-
2,7-dione undergoes photochemical ring closure to the respective bicyclic anhydride (Equation (4))
\( <86TL343> \).
Photochemical transformations of 3H-oxepin-2-ones resemble that of muconic anhydrides (see above), but are complicated by side reactions. Thus, UV photolysis of 3,3-dimethyloxepin-2-one (\( \sim 20^\circ C \), in acetone) gives besides the expected bicyclic lactone (19), an isomeric by-product (20); the yield of the latter was increased with increasing temperature (Equation (5)) \( 84JCS(P1)769 \). On 2-acetyl-naphthalene-sensitized photolysis of 3-acyl-3-methyloxepin-2-ones, the 1,5-acyl shift plays an important role giving, for example, 7-acetyl-3-methyloxepin-2-one, as the main product \( 85JCR(S)70 \).

Dihydrooxepines with two isolated C\( =\)C bonds can undergo selective transformations of only one, for example ethyl 3,4-dihydrooxepin-2-carboxylate on treatment with magnesium in methanol at room temperature affords in high yield (90\%) the product derived from the reduction of \( \alpha,\beta \)-unsaturated ester fragment, i.e. ethyl 2,3,4,5-tetrahydrooxepin-2-carboxylate \( 87TL5287 \).

### 9.02.6.2 Tetrahydrooxepines

Hydroboration of 2,3,4,5-tetrahydrooxepin was studied and compared with that of 2,3-dihydrofuran and \( \Delta^2 \)-dihydropyran as well as with their sulfur and carbocyclic analogues \( 85JOC5583 \). Boron is exclusively directed to the 3 position which is probably controlled by a strong mesomeric effect of the ring oxygen.

Metallation of 2,3,4,5-tetrahydrooxepin with Bu\(^n\)Li or BuLi leads to 7-lithio-2,3,4,5-tetrahydrooxepin, i.e. vinylic deprotonation occurs \( 82JOC3094 \). It is of interest that 2,3-dihydrooxepin, like 2,5-dihydrofuran, undergoes allylic deprotonation. The readily available trimethylsilyl ketene acetal of \( \epsilon \)-caprolactone is a convenient intermediate for the synthesis of 3-RO-substituted \( \epsilon \)-caprolactones (R is acyl or tosyl) using, as other reagents, lead(IV) carboxylates \( 83JOC4940 \) or [hydroxy(tosyloxy)iodo]benzene \( 89JOC1101 \), respectively.

Several interesting and effective syntheses of acyclic and carbocyclic natural products are based on (Z)-4-hexenolide and its substituted derivatives. In particular, this unsaturated lactone regioselectively reacts with diorganocuprates to give (Z)-4-alkenoic acids in high yields; this transformation was used for the simple synthesis of cis-jasmone \( 84CL1795 \). The other useful reagents for ring opening of (Z)-4-hexenolide are allylsilanes in the presence of trimethylxonium fluoroborate \( 84TL3213, 88BCJ4051 \). The importance of such transformations can be demonstrated by the stereo-selective synthesis of methyl (Z)-nona-4,8-dieneoate (Equation (6)).

\[
\begin{align*}
\text{O} & \quad + \quad \text{TMS} \\
\text{Me}_2\text{O}^+\text{BF}_4^- \quad \text{CH}_2\text{Cl}_2, 20^\circ C & \quad 87\% \\
& \quad \text{CO}_2\text{Me}
\end{align*}
\]

Ketene acetals obtained from unsaturated lactone enolates on mild thermolysis undergo the Claisen rearrangement leading to cis-2-alkenylcycloalkanecarboxylic acids \( 82JA4030 \). Starting from 4-hexenolides, substituted 2-cyclopropanecarboxylic acids, in particular, (−)-cis-chrysanthemic acid (Scheme 5) can be prepared \( 84T2831, 85JOC707, 85TL3503 \).

\[
\begin{align*}
\text{O} & \quad \text{LDA} \\
& \quad \text{RCI} \\
& \quad \text{Scheme 5}
\end{align*}
\]

\( R = \text{TBDMS}, \text{TBDPS}, m-\text{CH}_2\text{C}_6\text{H}_4\text{OPh} \)
Δ²-Unsaturated lactone, 2-hexenolide, enters as a dipolarophile 1,3-dipolar cycloaddition reaction with Δ¹-piperidine giving a new heterocyclic system, 1H-oxepino[3′,4′:4,5]isoxazolo-[2,3-a]pyridin-1-one (Equation (7)) \( <90\text{MRC947} > \).

2,3,4,5-Tetrahydrooxepin-2-yl acetate undergoes “head-to-tail” polymerization promoted by chromium carbene complexes \((\text{CO})_2\text{Cr} : \text{CRPh} \), where \( \text{R} = \text{Ph} \) or \( \text{OMe} \) \( <85\text{MOC279} > \).

\[
\begin{align*}
\text{N}^+ \text{O}^- & + \quad \text{O} & \rightarrow & \quad \text{N}^+ \text{O}^- \text{O} \quad \text{O} \\
(7)
\end{align*}
\]

9.02.6.3 Oxepanes, \( \varepsilon \)-Caprolactone, and Adipic Anhydride

\( \gamma \)-Ray induced addition of oxepan to fluorinated alkenes is described \( <85\text{JCS(P1)2215} > \). The reaction proceeds with 100% conversion and gives, in the case of perfluoropropene, 2-(2-\( H \)-hexafluoropropylo)oxepin in 95% yield. As mentioned above, \( \varepsilon \)-caprolactone is easily converted to the corresponding trimethylsilyl ketene acetal. Using trimethylsilyl triflate and triethylamine, trimethylsilyl acetal of cyclic trimethylsilyl-substituted ketene \( (21) \) can be prepared \( <83\text{LA816} > \).

Treatment of \( \varepsilon \)-caprolactone with \( \text{N,N-Bis(trimethylsilyl)} \)lithium amide and then with \( \text{N-phenyl} \)triflimide affords 2-triflyloxy-2-hexenolide \( (22) \). The latter is obtained in 89% yield \( <89\text{CL1313} > \) and can be regarded as a key intermediate in the syntheses of diverse 2-substituted 4,5,6,7-tetrahydrooxepines. For instance, reactions of \( (22) \) with lithium dialky- or diphenylcuprates result in 2-butyl-substituted derivatives \( (23; \text{R} = \text{Alk, Ph} \) \( <89\text{CL1313} > \), while analogous interaction with hexamethyldistannane gives 2-trimethylstannyl-4,5,6,7-tetrahydrooxepin \( (23; \text{R} = \text{SnMe₃} \) \( <91\text{SL197} > \).

\[
\begin{align*}
(21) & \\
(22) & \\
(23) & \\
(24)
\end{align*}
\]

Refluxing \( \varepsilon \)-caprolactone in carbon tetrachloride in the presence of triphenylphosphine leads to the formation of 2-dichloromethyleneoxepin \( (24) \) \( <82\text{JAP(K)53425} > \). \( \text{O-Alkylation} \) of \( \varepsilon \)-caprolactone gives the respective salt, which on treatment with sodium hydrosulfide undergoes scission of \( \text{exo-} \)or \( \text{endo-} \)—\( \text{O} \) bonds (Scheme 6) with the formation of \( \varepsilon \)-thionocaprolactone and alkyl \( \omega \)-hydroxy-thionocaproate, respectively \( <86\text{JA6683} > \).

The reaction of adipic anhydride with \( (\text{a-ethoxycarbonyl} \text{ethylidene}) \text{triphenylphosphorane} \) \( <87\text{BCJ689} > \) gives \( \text{endo-enol} \) \( \varepsilon \)-lactone, namely 6-(\( \text{a-ethoxycarbonyl} \text{ethyl} \)hex-5-enolide in low yield accompanied by several ring-opening products.

\[
\begin{align*}
\text{Et}_3\text{O}^+\text{BF}_4^- & + \quad \text{O} & \rightarrow & \quad \text{O}^+ \text{Et} \quad \text{BF}_4^- \\
\text{NaSH} & \rightarrow & \quad \text{O} & \quad \text{S} & \quad + & \quad \text{H} & \quad \text{O} \quad \text{E} \quad \text{O} \\
\text{Scheme 6}
\end{align*}
\]

9.02.7 RING SYNTHESSES FROM ACYCLIC COMPOUNDS

Cyclization reactions giving oxepines and oxepanes are classified here according to the number of atoms in starting compounds used for building the seven-membered ring and the nature of bonds formed. In some cases, acyclic precursors are prepared from cyclic starting compounds. If such precursors are isolated before cyclization, the respective reactions are considered here; in other cases they are discussed in Section 9.02.8. Syntheses of annelated oxepines are also included if the existing ring remained unchanged.
9.02.7.1 Intramolecular Cyclizations

9.02.7.1.1 Cyclizations with formation of ester C—O bonds

Seven-membered unsaturated lactones can be prepared in high yields by the cyclization of an appropriate \( \omega \)-hydroxyalkenoic acid, for example the available 3,3,6,6-tetramethylhex-4-enoic acid gives the respective lactone in 90% yield on simple contact with silica gel under column chromatography conditions (Scheme 7) \( \langle 84T2831 \rangle \).

\[
\begin{align*}
\text{CO}_2\text{H} & \quad \text{CO}_2\text{H} \\
\text{H}_2\text{Pd/BA}_2\text{SO}_4 & \\
\text{CO}_2\text{H} & \quad \text{CO}_2\text{H} \\
\text{SiO}_2 & \\
\text{HO} & \quad \text{O}
\end{align*}
\]

Scheme 7

Mukaiyama cyclization promoted with 2-chloro-1-pyridinium iodide in boiling methylene dichloride \( \langle 87JOC5296, 92JOM(431)335 \rangle \) was used for the formation of seven-membered alkynic lactones with the triple bond stabilized by complex formation from respective alkynic hydroxy acids (Equation (8)).

Refluxing 4-(5-aryl-2-oxo-4-pyrrolinyl-3-idene)butyric acids with acetic anhydride gave the corresponding pyrrolo-3,4-dihydro-2-oxepinones, while similarly substituted crotonic acids gave pyrrolo-2-oxepinones \( \langle 87AKZ189 \rangle \).

\[
\begin{align*}
\text{HO} & \quad \text{CO}_2\text{H} \\
\text{PhOS} & \quad \text{CO}_2\text{Me} \\
\text{Et}_3\text{N} & \\
\text{PhOS} & \quad \text{O}
\end{align*}
\]

Scheme 8

9.02.7.1.2 Cyclizations with formation of ether C—O bonds

The treatment of dimethyl (3-hydroxy-3-methylpent-4-ynyl)malonate with phenylsulfonyl chloride and triethylamine in ether leads (via the respective allene sulfoxide) to a uniquely substituted 4,5-dihydrooxepin (Scheme 8) \( \langle 87CC1718 \rangle \).

An interesting route to tetrahydrooxepines, formed in good yields (50–70%), uses the TiCl_4-promoted reaction of O-silylated alkynic alcohols with aliphatic aldehydes \( \langle 90CC967 \rangle \). As minor products, dienic carbinols are formed. The mechanism of this synthesis is shown in Scheme 9.

The oxidative ring closure of allylsilanes with ceric ammonium nitrate \( \langle 88T3983 \rangle \) should also be mentioned which gave mixtures (~1:1) of 2,5,6,7-tetrahydrooxepines with 2-alkenyltetrahydrofurans. Simple dehydration of 4-hydroxy-3-(4-hydroxy-3-alkylbutyl)coumarines with Amberlyst 15 leads to the respective annelated tetrahydrooxepines in 50–70% yield \( \langle 88JHC647 \rangle \).

An effective synthesis of oxepanones is based on rhodium carbenoid-mediated cyclizations of
appropriate diazocarbonyl compounds \( \langle 86\text{TL}1403, 88\text{JCS(P1)}1417, 89\text{JCS(P1)}721, 89\text{JCS(P1)}2473 \rangle \). Starting compounds can be obtained either on alkylation of the dianion of methyl acetoacetate with the Bu'Me₂Si-protected \( \alpha,\omega \)-haloalcohols, followed by diazo transfer and desilylation or on treatment of \( \delta \)-valerolactones with \( \alpha \)-lithiated diazocetates. The key step is intramolecular carbene insertion into the O—H bond, which proceeds after the treatment of diazo carbonyl compound with rhodium diacetate (Equation (9)); the yields reach \( \sim 80\% \). Starting from \( \delta \)-valerolactones and \( \alpha \)-lithiated diazomethane phosphonate or diazomethyl phenyl sulphone the respective 2-phosphorylated or phenylsulfonylated 3-oxepanones have been obtained; the latter are versatile intermediates for syntheses of various functionalized oxepanes \( \langle 91\text{JCS(P1)}1 \rangle \). Similar cyclization of 1-diazo-2,6-dioxoheptyl phenyl sulphone affords 7-methyl-2-phenylsulfonyl-2,3,4,5-tetrahydrooxepin-3-one \( \langle 87\text{TL}6045 \rangle \).

\[
\begin{align*}
\text{HO} & \quad \text{R} & \quad \text{CO}_2\text{R} \\
\begin{array}{c}
\text{R} = \text{H, alk}
\end{array} & \quad \text{N}_2 & \quad \text{Rh(OAc)}_2
\end{align*}
\]

9.02.7.1.3 Cyclizations with formation of carbon–carbon bond

In the formation of carbon–carbon bonds, cyclization reactions of various types are used. As an example of electrophilic cyclization involving formation of carbon–carbon bonds and leading to tetrahydrooxepines, the acetal–alkyne condensation \( \langle 88\text{TL}6365 \rangle \) mediated by Lewis acids can be noted (Scheme 10).
The acetal-alkene cyclization (Scheme 11) proceeds readily (60–70% yields) but gives mixtures (~1:1) of diastereoisomeric tetrahydrooxepines bearing halogenated side chains (25). However, halogen reduction results in only cis-isomers (26) in high yields (up to 85%). When a halogen atom is absent in an acetal molecule, the preparation of tetrahydrooxepines proceeds highly stereospecifically; the yields are up to 85%.

Scheme 11

Palladium-catalyzed cyclizations of bromodialkenyl ethers, in which the key step is vinylic substitution of bromine, result in low to moderate yields of tetrahydrooxepines and methyleneoxepanes. γ,δ-Unsaturated seven-membered lactones are prepared in 50–60% yields from 2-phenylthio-3-butenyl diazomalonates on treatment of the latter with rhodium acetate; the reaction involves a [2,3]-sigmatropic rearrangement of the generated cyclic allylsulfonium ylides.

Anodic oxidation of Bu₃Sn-protected unsaturated hemi-3-acetal (27) with tetrabutylammonium fluoroborate, as the supporting electrolyte, gave fluorinated oxepane (28) (61%) and its dehydrofluorination product (29) (28%).

Asymmetric carbonyl-ene cyclization of alkenyloxy-substituted aldehydes afforded six- and seven-membered cyclic ethers of high enantiomeric purity, for example (R)-(30) possessed a 91% ee (Equation (10)), when chiral 2,2'-dihydroxy-1,1'-binaphthyl-based titanium perchlorate was used as a catalyst.

Several cycloaddition reactions leading to fused bi- and triheterocyclic systems were used for the preparation of annelated hydrooxepines such as oxepino[3,4-c]isoxazole and oxepino[5,4,3-hi]indolizine. In photochemical conversion of 5-(p-methoxyphenyl)hept-5-enyl phenanthrene-5-carboxylate, two intramolecular [2 + 2] cycloaddition reactions involving alkene double bonds compete with either the 5,6-C=O bond of phenanthrene or the ester C=O bond, the latter giving phenanthryl-substituted oxetano[2,3-b]oxepan which undergoes degradation with loss of acetaldehyde giving 3-(p-methoxyphenyl)-2-phenanthr-5-yl-Δ²-tetrahydrooxepin. 3-(p-Methoxyphenyl)-2-phenanthr-5-yl-6,7-dihydrooxepin has been formed in 57% yield on photolysis of 5-(p-methoxyphenyl)pent-4-enyl phenanthrene-5-carboxylate.

An intramolecular Wittig reaction was used in the synthesis of an α,β-unsaturated seven-membered lactone from (5-formyl-2-oxopentylidene)phosphorane; however, the product
appeared to be a mixture (~1:1) of isomeric \( \Delta^2 \)- and \( \Delta^3 \)-lactones (Scheme 12), as a result of an equilibrium in the presence of a base (86JOC2830).

An intramolecular Wadsworth–Emmons reaction of respective phosphonates (Equation (11)) gave substituted 2,3,4,5-tetrahydrooxepines (91TL6947, 92T3991).

\[
\begin{align*}
\text{CHO} & \quad \text{PPh}_3 \\
& \quad \rightarrow
\end{align*}
\]

Scheme 12

\[
\begin{align*}
\text{O} & \quad \text{(EtO)}_2 \text{P} \\
& \quad \text{NaH} \\
& \quad \rightarrow
\end{align*}
\]

9.02.7.2 Intermolecular Ring Formation

Decomposition of ethyl diazopyruvate over Cu(acac)_2 in boiling benzene solution containing 2-methoxybuta-1,3-diene (83JOC3047) yielded ethyl 5-methoxy-5-vinyl-4,5-dihydro-2-furoate (78%) and a small amount (9%) of ethyl 5-methoxy-4,7-dihydrooxepin-2-carboxylate. It is important to note that the latter is a highly unstable compound and undergoes quantitative conversion into the former upon chromatography on silica gel. A similar reaction (Equation (12)) of ethyl diazopyruvate with 1,3-butadiene catalyzed by rhodium acetate gave a mixture of ethyl 4,7-dihydrooxepin-2-carboxylate (31) (26%), ethyl trans-(2-vinylcyclopropyl)glyoxylate (32) (35%) and 5-vinyl-4,5-dihydro-2-furoate (4%). The possible source of oxepin (31) could be its equilibrium with cis-(32), which is known to be shifted to (31) (87HCA2159).

\[
\begin{align*}
\text{CHO} & \quad \text{N}_2 \\
& \quad \rightarrow
\end{align*}
\]

The reaction, probably involving carben formation, of acrolein with ethyl \( \alpha \)-bromocrotonate, initiated by lithium diisopropylamide, generates \( \alpha \)-carbanion of ethyl \( \alpha \)-bromovinylacetate in the first step affording ethyl 4,5-dihydrooxepin-2-carboxylate, as one of products (Equation (13)) (86JOC4746).

The cycloaddition of carbon suboxide with 4-oximinopentanol (87H(26)1619) affords oxepines. On treatment of 8-hydroxynaphthalene-1-carboxaldehydes with DMA–POCl, complex 2-dimethylaminonaphth[1,8-\( bc \)]oxepinium salts are formed (86ZOR1487).

\[
\begin{align*}
\text{CHO} & \quad \text{Br} \\
& \quad \rightarrow
\end{align*}
\]

9.02.8 RING SYNTHESIS BY TRANSFORMATION OF ANOTHER RING

Many ring syntheses of oxepines and hydrogenated oxepines by the transformation of other rings are based on pericyclic reactions (88S569). Below are presented various synthetic methods, which are classified by the nature and size of the starting ring.
9.02.8.1 Synthesis from Carbocyclic Compounds

9.02.8.1.1 By formation of seven- from three-membered rings

Rhodium(I)-catalyzed reaction of phenyl 2-propylcycloprop-2-en-yl ketone with terminal alkynes gives 2-alkyl-4-propyl-7-phenyloxepines (Scheme 13). The reaction involves the formation of a rhodium-carbene complex, which undergoes a $[2 + 2]$ cycloaddition with a terminal ethyne; the resultant rhodacycle rearranges by a 1,5-sigmatropic shift, followed by reductive elimination of rhodium $^{<92JA5881>}$.

\[
\begin{array}{c}
\text{O} \\
\text{Ph} \\
\text{Pr} \\
\text{Ph} \\
\text{R} \\
\text{Pr} \\
\text{O} \\
\text{Rh} \\
\text{L}_n \\
\text{Pr} \\
\text{Pr} \\
\text{I} \\
\text{R} \\
\text{R} \\
\text{O-Rh} \\
\text{Pr} \\
\text{Rh-L}_n \\
\text{Pr} \\
\text{Pr} \\
\text{I} \\
\text{R} \\
\text{R} \\
\end{array}
\]

Scheme 13

Swern oxidation of 2-alkenyl-2-alkylsiloxy cyclopropylcarbinols involves a 3,3-sigmatropic rearrangement of the aldehydes formed and gives functionalized 2,5-dihydrooxepines (Scheme 14) in high yields $^{<93SL27>}$.

Thermolysis of vinyl-1,1-cyclopropanedicarboxylic acid affords (Z)-4-hexenolide besides the $\gamma$-vinyl-$\gamma$-butyrolactone $^{<86JAP(K)0727>}$.

\[
\begin{array}{c}
\text{TBDMS-O} \\
\text{R}^2 \\
\text{R}^1 \\
\text{OH} \\
\text{(COCI)}_2 \\
\text{DMSO, Et}_3N \\
\text{TBDMS-O} \\
\text{R}^2 \\
\text{R}^1 \\
\text{O} \\
\text{TBDMS-O} \\
\text{R}^1 = H, \text{Me, alk; R}^2, \text{R}^3 = H, \text{Me} \\
\end{array}
\]

Scheme 14

9.02.8.1.2 By formation of seven- from four-membered rings

Formally, this type of transformation can be illustrated by the known syntheses of 4,5-dihydrooxepin from bicyclo[2.2.0]hex-2-ene $^{<71JAm102, 76JOC2028>}$ including double-bond epoxidation and rearrangement of the intermediate tricycle (Scheme 15).

Similar syntheses of perfluorinated dihydrooxepin and 4,5-(difluoromethylenedioxy)-hexafluorodihydrooxepin are also known $^{<79JOC2813>}$. It should be mentioned that no equilibria with respective cyclohexadiene oxides were observed for the fluorinated dihydrooxepines.

\[
\begin{array}{c}
\text{O} \\
\text{O} \\
\text{O} \\
\text{O} \\
\text{O} \\
\text{O} \\
\end{array}
\]

Scheme 15

9.02.8.1.3 By formation of seven- from five-membered rings

One of the routes from five-membered carbocycles to seven-membered oxygen O-heterocycles is the oxidation of 6-monosubstituted and 6,6-disubstituted fulvenes with singlet oxygen to give the
respective 2(3H)-oxepinones (Scheme 16) \( \langle 71 \text{HCA913}, 72 \text{CL807}, 72 \text{JA1777} \rangle \). The yields are rather low (20–25%) but, when one of the \( R \) groups is alkyl and the other is either alkyl or aryl, 3\( H \)-isomers are the only 2-oxepinones formed in the photochemical oxidation. If, however, one of the \( R \) groups is hydrogen, besides the 2(3H)-oxepinones, their 7\( H \)-isomers are formed, probably as the result of photo-induced isomerization \( \langle 72 \text{CL807} \rangle \). The oxidation of 6,6-diarylfulvenes gives 3,3-diaryl-2-oxepinones as the only minor products \( \langle 74 \text{CL893} \rangle \), while the major ones are oxygenated carbocycles.

The transformation of benzvalene into oxepin–benzene oxide tautomeric system \( \langle 84 \text{CB2963} \rangle \) is another example of oxepin formation from five-membered rings.

![Scheme 16](image)

### 9.02.8.1.4 By formation of seven-from six-membered rings

Six-membered carbocycles often play the role of starting materials in the construction of the oxepin ring system; however, for many syntheses rather stable intermediates of a different nature are known, for example those with fused six-membered carbocycles and three-membered oxygen heterocycles. The use of such systems is described in the next section. Here, several other transformations are mentioned. Some of them also may have heterocycles as intermediates but the latter are unstable under normal conditions or their structures were not studied in detail.

\( \delta,\delta \)-Dehydro-\( \delta \)-caprolactone was formed in the Baeyer–Villiger oxidation of the respective unsaturated six-membered ketone using platinum(II) complexes, as catalysts \( \langle 93 \text{OM148} \rangle \). Oxidation of \( o \)-quinones can serve as a method for the synthesis of substituted muconic anhydrides \( \langle 82 \text{OC3766}, 83 \text{CC518} \rangle \). This process can be illustrated by the preparation of trideuterated anhydride (33), which results from the action of monoperphthalic acid on the respective deuteroquinone (Equation (14)) \( \langle 89 \text{CC1629} \rangle \).

![Equation 14](image)

Another important route to muconic anhydrides is the oxidation of 3,5-disubstituted catechols by molecular oxygen catalyzed by iron(III) salts \( \langle 87 \text{CL719}, 88 \text{JA8085}, 91 \text{JA9200} \rangle \) and heteropolyvanadates \( \langle 87 \text{JMOC57} \rangle \) as well as by a ruthenium dichloride–triphenyl phosphine complex \( \langle 82 \text{JA1433}, 82 \text{JAP(K)108033} \rangle \); the mechanism of the process is a model for the action of catechol 1,2-dioxigenase \( \langle 86 \text{JA2921}, 88 \text{JA8085}, 91 \text{JA9200} \rangle \).

\( p \)-Benzoquinone \( O \)-oxide (34) was matrix isolated and shown to be a real intermediate in the reaction of cyclohexadienone carbene (35) with triplet oxygen. This reaction gave the respective dioxiranes (36), which isomerize further to the seven-membered unsaturated ketolactones (37) (Scheme 17). Similar transformations were studied also for some substituted ketolactones \( \langle 88 \text{OC2091}, 92 \text{CB1851} \rangle \).

Photochemical rearrangement of chloroanil in the presence of cycloheptatriene or 1,3-cyclohexadiene gives the respective oxepin (38) in 70–95% yield (Equation (15)), while in the presence of
Oxepanes and Oxepines

\[
\text{cyclohexene the [2 + 2] cycloadduct of the latter with chloroanil at one of its C\(=\)O bonds is also formed} \quad \langle 87\text{MI 902-01} \rangle.
\]

The formation of oxepines from some \(p\)-quinoid compounds is known. Thus, peroxide bond cleavage in 2,6-di-\(t\)-butyl-4-hydroperoxy-4-methylcyclohexa-2,5-diene-1-one with sperm whale myoglobin and myoglobin mutants gives 4,6-di-\(t\)-butyl-2-hydroxy-2-methyloxepin-4-one and 4,6-di-\(t\)-butyl-2-methyleneoxepin-4-one \(\langle 92\text{JA9744} \rangle\). It is of interest that the dehydration product of 2,6-di-\(t\)-butyl-1-\(p\)-methoxyphenyl-4-phenylcyclohexa-2,5-diene-1,4-diol has the 3,7-di-\(t\)-butyl-5-phenyl-2-\(p\)-tolyloxepin structure \(\langle 82\text{CB385} \rangle\).

 Peroxidation of cyclohexen-3-one followed by the treatment of peroxide formed with benzoic anhydride and 4-dimethylaminopyridine (Scheme 18) leads to hexen-5-olide in 70\% yield \(\langle 84\text{TL2687} \rangle\).

9.02.8.2 Synthesis from Heterocyclic Compounds

9.02.8.2.1 By formation of seven-from three-membered rings

Synthesis of benzene oxides, which are in equilibrium with oxepines, is one of the most valuable methods for their preparation. As an example of its potential, a rather simple three-step synthesis of 2,7-diphenyloxepin can be given (Scheme 19) \(\langle 86\text{JOC2784} \rangle\). The equilibrium of the latter with the respective benzene oxide is shifted to the side of oxepin, but treatment of the product with trifluoroacetic acid quantitatively gives 2,6-diphenyloxenol.

The same preparative route can be illustrated (Scheme 20) by the synthesis of one of less stable oxepines, 2-vinyloxepin \(\langle 82\text{TL1185} \rangle\).
The perfluorinated oxepin has been prepared in this manner, but the content of the oxepin in the equilibrium mixture was very low \(<90JA6715\). A respective fused oxepin was prepared via dibenz[a,j]anthracene 3,4-oxide \(<90JCS(P1)2079\).

Some 7-oxabicyclo[4.1.0]heptanes bearing unsaturated substituents at the 1 position, for example 5,6-epoxy-5,6-dihydro-\(\beta\)-ionone, gave 2,7-dialkylideneoxepines (Equation (16)) under flash vacuum thermolysis at 390–585°C, the process was reversed by chromatography on silica \(<85HCA1089\). Similar results also gave photochemical reactions of the same compounds \(<86HCA555, 90JCS(P1)855\).

The transformation is general for different \(\alpha, \beta\)-unsaturated \(\gamma, \delta\)-epoxy ketones, for example epoxycyclohexenones \(<77JOC3635, 77TL1641\>) and epoxymethylene cyclohexanes \(<83HCA2489\>). Its mechanism is reminiscent of the above photooxidation of 6,6-disubstituted fulvenes (Scheme 21).

All R groups are H or one of them \(R_1, R_2, R_4\) is H, while all others are Me.

4,5-Dihydrooxepines are the products of Cope rearrangement of cis-2,3-divinyloxiranes (Equation (17)) \(<89T3021, 90JOC3975, 91TL157\>.

The role of one of the vinyl groups can be played by a double bond of furan ring \(<89T3021\>, the rearrangement results in the formation of a dihydrofuro[3,2-\(c\)]oxepin. Sulfur dioxide extrusion from tricyclic epoxide obtained from 3-thiabicyclo[3.2.0]hept-6-ene 3,3-dioxide (Scheme 22) affords 4,5-dihydrooxepin in 55% yield \(<82CC1164\).
Thermolysis of trans-2,3-divinyloxiranes to oxepines \(<91TL7637>\) can be regarded as proceeding via a carbonyl ylide, which can be trapped by dimethyl acetylenedicarboxylate (Scheme 23).

\[
\text{TMS} - \text{Me} - \text{MeO} - \text{Me} - \text{CO}_2\text{Me}
\]

\[
\text{TMS} \quad \overset{145 \degree C}{\longrightarrow} \quad \text{TMS} - \text{Me} - \text{Me} - \text{CO}_2\text{Me}
\]

\[
\text{TMS} - \text{CO}_2\text{Me}
\]

**Scheme 23**

exo-6,7-Diaza-3-oxatricyclo[3.2.2.0^1,4]non-6-ene gives 4,5-dihydrooxepin on a thermal extrusion (> 180 °C) of nitrogen, while the endo-isomer forms a Δ^2-cyclohexenone \(<90TL5129>\).

Monosubstituted oxiranes ring open on interaction with the dianion of 4-(phenylsulfonyl)-butanoic acid and then cyclize by the addition of trifluoroacetic anhydride to give oxepan-2-ones, as cis-/trans-mixtures \(<92SC239>\).

Tetrahydrooxepinols are formed in moderate yields on cyclization of carbanions formed from allyl glycicyl ethers; the process competes with the formation of isomeric (vinlyloxetanyl)carbinols \(<88CC625,90TL3501>\). The mechanism has been rationalized as shown in Scheme 24.

Directed ring opening of bicyclic oxiranylcarbinyl radicals (Scheme 25) affords tetrahydrooxepines in 50–70% yields \(<92SL987>\).

**Scheme 24**

**Scheme 25**

9.02.8.2.2 By formation of seven- from five-membered rings

The most efficient syntheses of oxepines from five-membered O-heterocycles are based on Diels–Alder reaction of furans with alkynes, photolysis of 7-oxanorbornadienes obtained to respective 3-
oxaquadricyclanes, and thermolysis of the latter \(84\text{CB}2422, 86\text{CB}297, 86\text{CB}589, 87\text{CB}775, 91\text{CB}2465\). This route can be illustrated by Scheme 26 \(87\text{CB}775\).

![Scheme 26](image)

As a specific example of such syntheses, the preparation of \([6]-3,6\)-oxepinophane starting from furan and cyclooctyne \(87\text{CB}769\) should be noted. The formation of 2,7-diethyl-3,4,5,6-tris(trifluoromethyl)oxepin from 2,5-diethyl-3,4-di(trifluoromethyl)furan and di(trifluoromethyl) ethyne is also of interest \(92\text{JHC}113\).

The synthesis of oxepino[2,3-\(d\)]isoxazole system from dimethyl acetylenedicarboxylate and substituted furo[3,4-\(d\)]isoxazole involves Diels–Alder reaction as the key step (Scheme 27) \(91\text{TL}1161\).

In an elegant synthesis of naphtho[1,8-\(b,c\)]oxepin, only one carbon atom of the furan ring is used for construction of oxepin cycle (Scheme 28) \(86\text{AJC}635\).

![Scheme 27](image)

Another route from five-membered \(O\)-heterocycles to oxepines uses 2,3-dihydrofurans as starting materials and involves their [2 + 2] cycloaddition reaction with ethyne or ethylene compounds, followed by cleavage of bicyclic compounds formed by thermolysis or Lewis acid catalysis \(83\text{CB}1691, 87\text{TL}1501, 92\text{JOC}5102\). These transformations are presented in Scheme 29 by starting from dimethyl acetylenedicarboxylate and 2,3-dihydrofuran or its 5-substituted derivatives \(87\text{TL}1501\).

![Scheme 29](image)
9.02.8.2.3  By formation of seven- from six-membered rings

An elegant route to oxepines starts with pyrill salts, which add lithium derivatives of electrophilic diazoalkanes giving the respective 4-diazoethyl-4\(H\)-pyrans, which undergo practically quantitative ring enlargement catalyzed by allylpalladium chloride (Scheme 30) \(\langle 83\text{T}L5355, 85\text{CB}3700, 87\text{JOC}3851 \rangle\).

![Scheme 30](image)

2-Hexenolides can be obtained by ring enlargement of pentanolide-derived silyl ketene acetics under the action of carbenes \(\langle 85\text{T}2643, 86\text{JOC}2830, 90\text{JOC}4807, 90\text{TL}197 \rangle\). The transformation is illustrated by the preparation of 2-methyl-2-hexenolid in 60\% yield (Scheme 31) \(\langle 85\text{T}2643 \rangle\). Using dibromocarbene \(\alpha\)-halogenated 2-hexenolide can be prepared; its reductive deconjugation gave the 3-hexenolide (Scheme 32) \(\langle 86\text{JOC}2830 \rangle\).

![Scheme 31](image)

![Scheme 32](image)

2-Methyl-5,6-dihydro-2\(H\)-pyran in the Simmons–Smith reaction with diiodomethane and Zn–Cu couple gives a mixture of four compounds, the main component of which (50\%) is 2-methyl-2,5,6,7-tetrahydrooxepin \(\langle 87\text{KG}5449 \rangle\). Nitrogen elimination from 6-diazo-5-methyl-3-oxabicyclo[4.1.0]heptane in methanol solution leads to the formation of the unstable \(\text{trans}\)-\(\Delta^2\)-tetrahydrooxepin derivatives, i.e. 5-methoxy-5-methyl-3\((E)\)- and 3-methoxy-5-methyl-4\((E)\)-tetrahydrooxepin mixture, which undergo further transformations affording numerous products possessing few stable oxepines \(\langle 82\text{CB}220 \rangle\). \(\text{Di-t-butyl-substituted muconic anhydride is formed among other products on 5,7-di-t-butyl-1,4-benzodioxin oxidation with m-chloroperoxybenzoic acid} \(\langle 87\text{JHC}785 \rangle\).

Intramolecular Diels–Alder cycloaddition with inverse electron demand of 3-\((\text{hex-5-ynyloxy})\)-6-dimethylamino-1,2,4,5-tetrazine allows formation of the respective tetrahydrooxepino-[3,4-\(b\)]pyridazine in moderate yield \(\langle 87\text{CZ}16 \rangle\). Analogous cycloaddition of 3-\((\text{hex-5-ynyloxy})\)-5-trifluoromethyl-1,2,4-triazine gives 2-trifluoromethyl-5,6,7,8-tetrahydrooxepino[2,3-\(b\)]pyridine in 40\% yield \(\langle 89\text{AP}(322)561 \rangle\). It should be noted that cycloaddition of 3-\((\text{hex-5-ynyloxy})\)-5,6-diphenyl-1,2,4-triazine followed by oxidation with nitrobenzene at 210 °C leads to the corresponding tetrahydrooxepino[2,3-\(b\)]pyridine but only in 8\% yield \(\langle 86\text{T}L2747 \rangle\). As an intramolecular variant of a related synthesis, the preparation of 3,7-substituted \(5H\)-oxepin-2-ones in high yields from 6-oxo-1,3,4-oxadiazines and cyclopentene (Scheme 33) can be mentioned \(\langle 85\text{CB}2940, 87\text{TL}6429, 90\text{CB}2031 \rangle\).

2,5-Dihydrooxepino[3,2-\(a\)]carbazole derivatives are formed in moderate to rather high yields on photochemical rearrangement of pyronocarbazole alkaloids, for example mahanimbine \(\langle 88\text{T}L6625 \rangle\).
9.02.9 SYNTHESIS OF PARTICULAR CLASSES OF COMPOUNDS

Attempts to evaluate the synthetic potential of different preparative methods are made in Sections 9.02.7 and 9.02.8. In Tables 1–4, references are given to synthetic routes to several specific groups of oxepanes and oxepines. Most references were cited in the above sections. For completeness, those from CHEC-I were also included.

Table 1 Synthetic routes to monocyclic oxepanes.

<table>
<thead>
<tr>
<th>Type of compound</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxepan</td>
<td>64JOC123</td>
</tr>
<tr>
<td>2,7-Dialkyloxepanes</td>
<td>91JCS(P1)9</td>
</tr>
<tr>
<td>Tetrahydrooxepines</td>
<td>58JA3132, 60JA4087, 66TL5385</td>
</tr>
<tr>
<td>Dihydrooxepines</td>
<td>60JA4087, 64JOC1275, 69JA2815</td>
</tr>
<tr>
<td>Hydroxy-, alkoxy-, and acyloxyoxepanes</td>
<td>53JOC1356, 58CB1589, 58JA3064, 60JA4087, 65JOC335, 81JOC2267</td>
</tr>
<tr>
<td>Oxepanones and oxepanediones</td>
<td>30JA4110, 49JA2571, 58CB1589</td>
</tr>
<tr>
<td>Deuterated 3-methylmuconic anhydride</td>
<td>89CC1629</td>
</tr>
<tr>
<td>Optically active e-enantholactone</td>
<td>89S861</td>
</tr>
<tr>
<td>Seven-Membered alkynic lactones</td>
<td>87JOC5296, 92JOM(431)335</td>
</tr>
<tr>
<td>Fluorinated and polyfluorinated oxepanes</td>
<td>85JFC(30)189, 92JA7594</td>
</tr>
<tr>
<td>Polyfluoroalkyloxepane</td>
<td>85JCS(P1)2215</td>
</tr>
<tr>
<td>Other halooxepanes</td>
<td>60JA4087</td>
</tr>
<tr>
<td>Silylated oxepanone and hydrooxepins</td>
<td>91JCS(P1), 91TL157, 91TL7637, 92JOC7010</td>
</tr>
<tr>
<td>Stannylated hydrooxepin</td>
<td>91SL197</td>
</tr>
<tr>
<td>Phosphorylated oxepanones</td>
<td>91JCS(P1)1</td>
</tr>
<tr>
<td>Sulfonlated oxepanones</td>
<td>87TL6045, 91JCS(P1), 92SC239</td>
</tr>
</tbody>
</table>

Table 2 Synthetic routes to monocyclic oxepines.

<table>
<thead>
<tr>
<th>Type of compound</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxepin, alkyl-, and aryloxepines</td>
<td>67AG(E)385, 72B3080, 78JA6483, 78JOC2711</td>
</tr>
<tr>
<td>Vinylloxepines</td>
<td>82TL1185</td>
</tr>
<tr>
<td>Aminoalkyloxepines</td>
<td>80JOC3149</td>
</tr>
<tr>
<td>Hydroxyalkyloxepines and their esters</td>
<td>76TL1167, 78JA6483, 81JA898</td>
</tr>
<tr>
<td>Oxepin-carboxaldehydes</td>
<td>76TL1167, 81JA898</td>
</tr>
<tr>
<td>2-Acetyloxepin</td>
<td>67AG(E)385</td>
</tr>
<tr>
<td>Oxepin-carboxylic acids and their esters</td>
<td>67AG(E)385, 74JA1193, 74JOC2088, 76ACR378, 76TL1167, 77JOC2008, 79JA2470</td>
</tr>
<tr>
<td>Cyanooxepines</td>
<td>76ACR378, 76TL1167, 81JOC813</td>
</tr>
<tr>
<td>Oxepinalkanoic and -alkenoic acids and esters</td>
<td>81JOC1191</td>
</tr>
<tr>
<td>Fluorinated and polyfluorinated oxepines</td>
<td>83JCS(P1)2451, 90JA6715</td>
</tr>
<tr>
<td>Perfluoroalkyloxepines</td>
<td>76CB2823, 83JCS(P1)2451, 92JHC113</td>
</tr>
<tr>
<td>Other halooxepines</td>
<td>75JA4428, 87MI902-01</td>
</tr>
<tr>
<td>Silyloxepines</td>
<td>81JOC1817</td>
</tr>
</tbody>
</table>
Table 3 Synthetic routes to polycyclic oxepanes.

<table>
<thead>
<tr>
<th>Type of compound</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclopropaoxepanes</td>
<td>85HCA1089, 90JOC4807</td>
</tr>
<tr>
<td>Benzannelated hydrooxepines</td>
<td>25CB78, 53JOC801, 61JCS2516, 66CB634, 67CR(C)1665, 69TL2007, 91JHC1891</td>
</tr>
<tr>
<td>Dihydropyranth[1,8-bc]oxepine</td>
<td>86AJC635</td>
</tr>
<tr>
<td>4,5-Epoxypyanxen</td>
<td>60JA4087</td>
</tr>
<tr>
<td>Oxetanooxepan</td>
<td>90BCJ1049</td>
</tr>
<tr>
<td>Dihydrofurooxepin</td>
<td>89T3021</td>
</tr>
<tr>
<td>Tetrahydrooxepinobenzopyran</td>
<td>88HCC647</td>
</tr>
<tr>
<td>9-0xacyclo[4,2.1]non-6-ene</td>
<td>86HCA555</td>
</tr>
<tr>
<td>7,11-Dioxyabicyclo[4.4.1]undeca-8,10-diene</td>
<td>83HCA2489</td>
</tr>
<tr>
<td>Perfluorinated dihydrooxepino-1,3-dioxolane</td>
<td>79JOC2813</td>
</tr>
<tr>
<td>Tetrahydrooxepinoisoaxazole</td>
<td>91CB1181</td>
</tr>
<tr>
<td>Tetrahydrooxepino[2,3-b]pyridine</td>
<td>89AP(322)561</td>
</tr>
<tr>
<td>Dihydrooxepino[4,5-b]pyridine</td>
<td>87H(25)13</td>
</tr>
<tr>
<td>Tetrahydrooxepino[3,2-c]quinolin-6-one</td>
<td>89G367</td>
</tr>
<tr>
<td>Tetrahydrooxepino[2,3-c]pyridazine</td>
<td>87CZ16</td>
</tr>
<tr>
<td>Dihydrooxepino[4,5-d]pyridazine</td>
<td>83CB97</td>
</tr>
<tr>
<td>Dihydrooxepino[5,4,3-h]indolyzine</td>
<td>91CZ25</td>
</tr>
<tr>
<td>2,5-Dihydrooxepino[3,2-a]carbazoles</td>
<td>88TL6625</td>
</tr>
</tbody>
</table>

Table 4 Synthetic routes to polycyclic oxepines.

<table>
<thead>
<tr>
<th>Type of compound</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzannelated oxepines</td>
<td>65CJC3433, 65TL1299, 66CB634, 68JOC2591, 73CC37, 90JCS(P1)2079</td>
</tr>
<tr>
<td>peri-Annulated naphthoxepinium salt</td>
<td>86ZOR1487</td>
</tr>
<tr>
<td>ansa-Derivatives of oxepines</td>
<td>86CB297, 87CB769</td>
</tr>
<tr>
<td>Oxepino[2,3-d]isoxazole</td>
<td>91TL1161</td>
</tr>
<tr>
<td>Diethyropyranoxepin</td>
<td>84CB2422</td>
</tr>
<tr>
<td>Oxepino[4,5-c]pyridine</td>
<td>83CB97</td>
</tr>
</tbody>
</table>

9.02.10 IMPORTANT COMPOUNDS AND APPLICATIONS

9.02.10.1 Applications and Important Compounds of Oxepanes and Hydrooxepines

The most practically important compound from oxepanes is ε-caprolactone which is used as a monomer. Other oxepanes are considered following their structures from rather simple monocyclic to complicated polyheterocyclic systems.

Total synthesis of utero-evacuating oxepan, (−)-zoapatanol (39), has been described <81TL3027, 81USP4296035>. Deoxyzoapatanol derivatives, which are postimplant antigestational agents, have also been prepared in 24 steps <83USP4384126>.

From marine red seaweed of the Laurencia family, a group of metabolites was isolated whose structures are based on 2-propyl- and 2-ethyl-7-(hex-3-en-5-ynyl)-2,3,6,7-tetrahydrooxepin possessing chlorine or bromine atoms in the cycle or side chains. Among these compounds, are rogiolenynes A (40), B, C, D <92HCA303, 92HCA310>, laurepinacin (41) and iso-laurepinacin (42) <81TL4081>. Closely related isoprelaurefucin (43) having a 2,7-dioxabiclo[4,2.1]nonane skeleton (39).
Oxepanes and Oxepines

as well as trans-laurencenyne (82TL1475), a possible acyclic biosynthetic precursor of laurepinnacins (proposed in 81TL4081), are noteworthy.

Rather simple 4-methyl-2-(3-methylbuta-1,3-dienyl)-Δ4-tetrahydrooxepin and -oxepan isolated from fresh fruits and prepared by synthesis have been patented as perfuming and flavoring ingredients 90EUP371347. 3,6-Dialkyl-2-hexenolides have been claimed as cosmetic fragrant agents 88JAP(K)316776. Organoleptic uses have been suggested for 6-alkylhexenolides and 6-alkenylhexanolides 90EUP354000.

2-Carboxy-, 2-γ-carboxypollyl-, and 2-β-vinyl-substituted derivatives of 11-(aminoalkylidene)-6,11-dihydridibenzo[b,e]oxepin have been prepared and shown to have antiallergic activity 92CPB238, 92JMC2074.

Diterpene and sesquiterpene, seven-membered lactones (44), (45) were isolated from Melampodium longipilum 84P829 and Conyza hypolenca 91P575. Two oxepan diterpene bicyclic lactones were isolated from Melampodium diffusum 84P833. The anhydride of bis(5,6-methylenebiphenyl-2,2′-dicarboxylic acid was reduced to the respective dibenzoepinepinone, which, on the action of alkanols, gave alkyl 2′-hydroxymethylbiphenyl-2-carboxylates, which were claimed to be therapeutic agents for curing liver diseases 90EUP353358, 90JAP(K)48574.

A xanthone antibiotic, growth self-inhibitor chloromonilicin (46), was isolated from plant pathogenic fungi Monil Linia fructicola 86MI902-01. Surenolactone 82LA87, a tetranortriterpenoid A/B-dilactone with two fused seven-membered lactone units was isolated from Toona sureni (Meliaceae).

Numerous diketopiperazine antibiotics having a common partly hydrogenated oxepino[3,4-b]pyrrolo[1,2-q]pyrazine skeleton were isolated from fungi of Emericella 86MI902-02, 87H(26)475, 89MI902-01, 90CPB73, Aspergillus 86CC1495, 86JCR(S)302, and Ramichloridium species 90JAP(K)62880.

Polycyclic indo1e alkaloid augustilobine B has a tetrahydrooxepin moiety as one of the structural fragments 87MI902-02.

A vast amount of work has been devoted to structure elucidation and synthesis of polyster toxins from marine organisms, particularly, of brevetoxins 89JA6476, 90JA3040, 90JA3696, 90JA4988, 92CL1587, 92JA7935, for example hemibrevetoxin B (47), and gambriec acid 92JOC5448, all of which have oxepan ring as part of their fused polycyclic skeleton.
Pyran ring enlargement in a dihydrospectinomycin derivative gave modified antibiotics, homospectinomycins are derivatives of perhydrooxepino[2,3-b]benz-1,4-dioxane, which exhibited bactericidal activity <88JAN1445>.

9.02.10.2 Applications and Important Compounds of Oxepines

Natural monocyclic and annelated oxepines are not as numerous as their hydrogenated derivatives; however, as mentioned in CHEC-I, <84CHEC-I(7)547> they play an important role in biosynthesis and metabolism of monocyclic and polycyclic aromatic compounds. Some new data concerning natural oxepines is given below.

1-Methoxycarbonylbenzene oxide (48), the valence tautomer of 2-methoxycarbonyloxepin, was isolated from liquid cultures of wood-rotting fungus *Phellinus tremulae* <93TL1589>.

Dibenz[a,j]anthracene-3,4-oxide together with the respective oxepin (49) are mammalian metabolites of dibenz[a,j]anthracene, their synthesis is described in <90JCS(P1)2079>.

Cinereain (50), a metabolite with plant growth-regulating activity from *Botrytis cinerea*, is 1-isopropyl - 4 - isobutylidene - 2.11 - dioxo - 1,2,3,4 - tetrahydro - 1H - oxepino[3,2-g]pyrido[3,2-a]pyrazine <88ABC1725>.

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![Chemical Structures](47)

(47)

![Chemical Structures](48)

(48)

![Chemical Structures](49)

(49)

![Chemical Structures](50)

(50)