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1,3-Oxazine Derivatives

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I. Introduction

The last decade has brought a considerable increase of the number of papers concerned with 1,3-oxazine derivatives. This is due partly to the fact that these compounds show interesting reactivity. Hence, it was suggested recently that 1,3-oxazine derivatives (including benz-1,3-oxazine derivatives) should be used as chemotherapeutic agents.¹⁻⁹


311
Karrer\(^{10}\) thought that the dihydro-1,3-oxazine skeleton can possibly be formed in proteins during their transformation to polypeptides. Fodor\(^{11,12}\) and Fieser\(^{13}\) explained the stereospecific migration of acyl groups from N to O and vice versa in tropine alkaloids by an intermediate formation of a 1,3-oxazine ring.

II. Nomenclature

1,3-Oxazine, metoxazine (or mazoxin), consists of a ring of four carbon atoms, one oxygen, and one nitrogen atom; the two hetero atoms are in the 1,3-positions or "meta,"

\[ \begin{array}{c}
5 \quad 4 \quad N \\
6 \quad 2 \\
O
\end{array} \]

They can be further classified according to the degree of saturation and the position of double bonds. The fully saturated ring is tetrahydro-1,3-oxazine:

\[ \begin{array}{c}
H_2C \\
H_2C
\end{array} \]

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

The compounds with one double bond are dihydro-1,3-oxazines, and the structures shown in Fig. 1 are possible. The conformations of dihydro-1,3-oxazine rings are based on analogy with cyclohexene and also on the conformational analysis of several benzo-1,3-oxazine derivatives.


1,3-Oxazine derivatives with two double bonds can exist in three isomeric forms:

- **1,3-2-Oxazine** or **1,3-2H-oxazine** or **2H-1,3-oxazine**
- **1,3-4-Oxazine** or **1,3-4H-oxazine** or **4H-1,3-oxazine**
- **1,3-6-Oxazine** or **1,3-6H'-oxazine** or **6H-1,3-oxazine**

Of these, only a few representatives of 1,3-4H-oxazine are known in the literature.

III. Methods of Preparation of 1,3-Oxazine Derivatives

A general rule can be suggested for one of the principal ways of forming 1,3-oxazine derivatives. They can be formed from 1,3-substituted propane derivatives of general formula:

\[
X-\text{CH}_2-\text{CH}_2-\text{CH}_2-Y
\]

where

- \(X = \text{NHR}\) and \(Y = \text{OH, Cl, Br, OCOR', OCH}=\text{CH}_2, \text{COOR'}\)
- \(X = \text{NHCOR}\) and \(Y = \text{COOH}\)
- \(X = \text{N}_3\) and \(Y = \text{OH}\)
- \(X = \text{NH}--\text{C}=\text{N}\) and \(Y = \text{Br}\)
\[ X = \text{N} == \text{C} == \text{NR} \text{ and } Y = \text{OH} \\
X = \text{OH} \text{ and } Y = \text{OH} \\
X = \text{OH} \text{ and } Y = \text{OCONH}_2 \\
X = \text{OC}(\text{:NH})R \text{ and } Y = \text{Br}. \]

These compounds can react with various "cyclizing agents," described in the following.

In addition to the compounds just tabulated, a number of less typical methods can also be used to form 1,3-oxazine rings.

**A. TETRAHYDRO-1,3-OXAZINE DERIVATIVES**

The formation of 1,3-oxazine derivatives was reported for the first time by Kohn.\textsuperscript{14} It consisted in cyclizing 3-aminopropan-1-ol derivatives with aldehydes to yield tetrahydro-1,3-oxazine derivatives (1).

\[
\begin{align*}
\text{H}_3\text{C} & \text{C} \text{C} \text{CH}_3 \\
\text{H}_2\text{C} & \text{C} \text{C} \text{NHR} \\
\text{H}_3\text{C} & \text{C} \text{C} \text{OH} \\
\text{H}_3\text{C} & \text{C} \text{C} \text{R'} \text{CHO} \\
\end{align*}
\]

\[
\begin{array}{c}
\text{H}_3\text{C} \text{C} \text{C} \text{N} \text{R} \\
\text{H}_3\text{C} \text{C} \text{O} \text{R'} \text{CHO} \\
\end{array}
\]

(1)

The reaction was studied by a number of authors and both aldehydes and ketones were used as cyclizing agents.\textsuperscript{15-20}

It has been found\textsuperscript{15,16,21-27} that those derivatives of 3-aminopropan-1-ol react most readily which contain secondary amino and hydroxyl groups as in the original formation of (1). The reaction can be catalyzed by alkaline reagents, e.g., small amounts of potassium hydroxide.

3-Aminopropan-1-ol can react with formaldehyde to form the parent tetrahydro-1,3-oxazine (2) itself. With an excess of formaldehyde, a bicyclic compound (3) is obtained.\textsuperscript{29,28}

![Chemical structures](image)

It was recently shown\textsuperscript{29,30} that the formation of a Schiff's base is the first step of the reaction between 3-aminopropan-1-ol and an aldehyde. The action of acid chlorides, such as tosyl chloride, on the Schiff's base forms the N-acyl derivative of tetrahydro-1,3-oxazine.

Among various other ways of cyclizing 3-aminopropan-1-ol to a tetrahydro-1,3-oxazine derivative, an interesting reagent is acetylene under pressure\textsuperscript{31,32}:

![Chemical structure](image)

The product (4) is identical with that obtained from 3-aminopropan-1-ol and acetaldehyde.

Vinylbutoxyethyl ether can also be used for the cyclization in presence of mercuric salts\textsuperscript{33}:

![Chemical structure](image)

An interesting formation of a tetrahydro-1,3-oxazine derivative (5) occurs on reacting the vinyl ether of 3-aminopropan-1-ol with N,N-dimethylcarbamyl chloride.\textsuperscript{31}

\[
\begin{array}{c}
\text{H}_2\text{C} \quad \text{NH}_2 \\
\text{H}_2\text{C} \quad \text{C} \quad \text{O} \quad \text{H} \quad \text{CH}_2
\end{array}
\xrightarrow{\text{CICON(CH}_3)_2} 
\begin{array}{c}
\text{CON(CH}_3)_2 \\
\text{C}_3\text{H}_3
\end{array}
\]

(5)

One of the most extensively investigated groups of 1,3-oxazine derivatives is the 5-nitro derivatives of tetrahydro-1,3-oxazine. They were first prepared from 1-nitropropane, aqueous formaldehyde, and ammonia by Hirst \textit{et al.}\textsuperscript{34} and independently by Senkus\textsuperscript{35,36} from other primary nitroparaffins, formaldehyde, and primary amines. Numerous compounds of the general formula (6) were later prepared from primary nitroparaffins\textsuperscript{37-50}

\[
\begin{array}{c}
\text{R} \\
\text{O}_2\text{N} \\
\text{N} \\
\text{R'}
\end{array}
\]

(6)

In formula (6), R varies from CH\textsubscript{3} to C\textsubscript{15}H\textsubscript{31} when nitroparaffins

\textsuperscript{34} T. Urbański and E. Lipska, \textit{Roczniki Chem.} 26, 182 (1952).
\textsuperscript{40} D. Gürne and T. Urbański, \textit{Bull. acad. polon. sci., Classe III} 4, 221 (1956).
from nitroethane to 1-nitro-\(n\)-hexadecane were used.\textsuperscript{40,41,44,51–53} Commencing with nitromethane gave \(R = \text{CH}_2\text{OH}\) or \(H\).\textsuperscript{39,45}

The \(R'\) depends on the amine \(R'\text{NH}_2\) used in the reaction. When ammonia was used a bicyclic product (7) was formed from nitroethane.\textsuperscript{37}

\[
\begin{align*}
\text{H}_2\text{C} & \underset{\text{O}_2\text{N}}{\text{C}} \underset{\text{H}_2}{\text{C}} \underset{\text{N}}{\text{N}} \underset{\text{C}_2\text{H}_5}{\text{N}} \underset{\text{C}_2\text{H}_5}{\text{CH}_3} \\
\text{NO}_2 & \quad \text{NO}_2
\end{align*}
\]

(7)

1-Nitropropane and formaldehyde yielded in presence of ammonia two products of the general structure (6): the first with \(R = \text{C}_2\text{H}_5\), \(R' = \text{H}\) and the second with \(R = \text{C}_2\text{H}_5\), \(R' = -\text{CH}_2-\text{C}(\text{NO}_2)(\text{C}_2\text{H}_5)-\text{CH}_2\text{OH}\) (12).\textsuperscript{34} Higher 1-nitroparaffins, formaldehyde, and ammonia yielded only one product (6), \(R' = \text{H}\).

It has been found that the simplest method of preparing 5-nitrotetrahydro-1,3-oxazine derivatives consists in warming 2-alkyl-2-nitropropane-1,3-diol with formaldehyde and ammonia or primary amines:

\[
\begin{align*}
\text{R} & \underset{\text{O}_2\text{N}}{\text{C}} \underset{\text{CH}_2\text{O}}{\text{C}} \underset{\text{O}_2\text{N}}{\text{C}} \underset{\text{CH}_2\text{OH}}{\text{C}} \underset{\text{NH}_2\text{R'}}{\text{N}} \underset{\text{R'}}{\text{N}} \\
\text{O}_2\text{N} & \quad \text{CH}_2\text{O} \quad \text{NH}_2\text{R'}
\end{align*}
\]

(6)

When \(R = \text{CH}_2\text{OH}\), the reaction was successful only with primary amines, but not with ammonia which yielded only resinous products.

It was recently demonstrated by Eckstein et al.\textsuperscript{54,55} that the course of the reaction involves the formation of an \(s\)-triazine derivative (8)

from formaldehyde and the amine. The substance (8) acts as a source of formaldehyde and the amine when it reacts with 2-nitropropan-1,3-diol.

\[
3 \text{CH}_2\text{O} + 3 \text{NH}_2\text{R'} \rightarrow \text{(8)}
\]

All attempts failed to prepare 5-nitrotetrahydro-1,3-oxazine derivatives from nitromethane, ammonia and formaldehyde,\textsuperscript{56} acetaldehyde,\textsuperscript{57} or isovaleraldehyde.\textsuperscript{42}

The 2-substituted 5-nitrotetrahydro-1,3-oxazine derivatives (9) can be obtained by reacting aldehydes with 2-alkyl-2-nitro-3-aminopropan-1-ol (10) derivatives. By using various primary amines,

\[
\text{(10)}
\]

different 1,3-oxazines substituted in the 3-position have been prepared.\textsuperscript{35,36,38,39,44-47,49,58-62}

The great tendency of 2-nitro-3-aminopropan-1-ol derivatives to form 1,3-oxazine derivatives (e.g., 12) was demonstrated\textsuperscript{63} when it was attempted to acetylate a derivative of 2-nitro-3-aminopropan-1-ol (11).

\textsuperscript{56} S. Malinowski and T. Urbański, \textit{Roczniki Chem.} 25, 185 (1951).
\textsuperscript{60} T. Urbański and H. Piotrowska, \textit{Roczniki Chem.} 31, 553 (1957).
\textsuperscript{63} T. Urbański and B. Szczyciński, \textit{Bull. acad. polon. sci., Classe III} 4, 225 (1956).
A new method of preparing tetrahydro-1,3-oxazine derivatives (13 and 14) consists in reacting olefins with formaldehyde and ammonium chloride or hydrochlorides of primary amines.\(^\text{14-71}\)

\[
\begin{align*}
C_6H_5CH=CH_2 & + CH_2O + NH_4Cl \\
& \xrightarrow{\text{NaOH}} \\
\text{(13)} & + \text{(14)}
\end{align*}
\]

B. OXO AND THIONO DERIVATIVES OF TETRAHYDRO-1,3-OXAZINE

The 2-oxotetrahydro-1,3-oxazines can be classified as cyclic urethanes. They have been relatively extensively investigated, because of their expected biological activity.

The first preparation of a 2-oxotetrahydro-1,3-oxazine derivative


(15) was reported by Franchimont and Lublin. The reaction proceeded from a carbamate:

\[
\begin{align*}
\text{H}_2\text{C} & \text{NH}_2 \text{HNO}_3 \\
\text{H}_2\text{C} & \text{O} \text{CO} \\
\end{align*}
\]

(15)

Heating dicarbamates with anhydrous zinc chloride also gives 2-oxotetrahydro-1,3-oxazine.

\[
\begin{align*}
\text{H}_2\text{C} & \text{NHAr} \\
\text{H}_2\text{C} & \text{O} \text{CO} \\
\end{align*}
\]

A similar reaction of \(\gamma\)-bromopropyl derivatives under the influence of silver nitrate was described by Kohn as early as 1904. The 3-hydroxyketone formed from chloral and acetophenone can react with a chlorocarbamate to yield a pseudourethane which is probably a 4-hydroxy-2-oxotetrahydro-1,3-oxazine.

A number of 5-hydroxy-2-oxotetrahydro-1,3-oxazine derivatives can also be formed from glycide esters of carbamic acid:

\[
\begin{align*}
\text{C}_6\text{H}_5 & \text{NCOOCH}_2\text{C} & \text{H} \\
\end{align*}
\]

The same product (17) can be prepared from 3-chloropropan-1,2-diol.

---

72 A. P. N. Franchimont and A. Lublin, Rec. trav. chim. 21, 45 (1902).
75 J. S. Pierce and A. Adams, J. Am. Chem. Soc. 45, 790 (1923).
Some amides can also be converted to 2-oxotetrahydro-1,3-oxazines.\textsuperscript{79}

A number of simple reactions are now known which form 2-oxotetrahydro-1,3-oxazine (18). Here, also, 3-aminopropanol and some of its derivatives are frequently used. Cyclizing reagents are: carbonic acid esters in strongly basic medium,\textsuperscript{80-87} ethyl chloropropionate,\textsuperscript{22} trichloracetic esters,\textsuperscript{88,89} or phenyl isocyanate.\textsuperscript{87,90} An example of the first of these methods is:

\begin{equation}
\begin{array}{c}
\text{H}_{2}\text{C-} \\
\text{N'} \\
\text{R} \\
\text{R'} \\
\text{H} \\
\text{R''} \\
\text{OH} \\
\text{R''} \\
\text{O} \\
\end{array} + \text{CO(OR''\textsubscript{2})} \rightarrow \text{R''OH} \\
\text{R} \\
\text{N} \\
\text{C}_{6}\text{H}_{5} \text{O} \\
\end{equation}

The reaction is promoted by alcohohates or sodium hydride.

An interesting method of forming 2-oxo-3-phenyltetrahydro-1,3-oxazine (19) and its derivatives was recently given by Gulbins et al.\textsuperscript{91} It consists of heating a 2-oxo-1,3-dioxane with phenyl isocyanate:

\begin{equation}
\begin{array}{c}
\text{R} \\
\text{H} \\
\text{C} \\
\text{C} \\
\text{H}_{2} \\
\text{C} \\
\text{C} \\
\text{O} \\
\text{C} \\
\text{H} \\
\text{C} \\
\end{array} + \text{C}_{6}\text{H}_{5}\text{NCO} \rightarrow \text{LiCl} \rightarrow 220^\circ \\
\text{R} \\
\text{N} \\
\text{C}_{6}\text{H}_{5} \text{C} \\
\text{O} \\
\end{equation}

It has also been stated\textsuperscript{92} that malonic acid, benzaldehyde, and ammonia can react to form tribenzalidiiminemalonic acid which under the action of hydrochloric acid is transformed into 6-oxo-2,4-di-phenyltetrahydro-1,3-oxazine (20). This is the only known representative of the 6-oxotetrahydro-1,3-oxazines.

\[\text{C}_6\text{H}_5\]
\[\begin{array}{c}
\text{O} \\
\text{NH} \\
\text{O}
\end{array}\]
\[\text{C}_6\text{H}_5\]

(20)

2,6-Dioxotetrahydro-1,3-oxazine (21) can be obtained by reacting phosgene with $\beta$-amino acids\textsuperscript{93-97}:

\[\begin{array}{c}
\text{R}^1
\text{R}^2
\text{NHR}^3
\text{O}\text{C}\text{OH}
\end{array} + \text{COCl}_2 \rightarrow \]
\[\begin{array}{c}
\text{R}^1
\text{R}^2
\text{N}
\text{R}^4
\text{O}
\text{O}
\end{array}\]

(21)

An interesting method for preparing 2,6-dioxo-1,3-oxazine derivatives was described by Wasserman and Koch\textsuperscript{98} who stated that the five-membered ring of an $\alpha$-keto-lactam could be transformed into the 1,3-oxazine (22) by ozone followed by reduction with zinc.

\[\begin{array}{c}
\text{C}_6\text{H}_5
\end{array} + \text{O}_3 \rightarrow \]
\[\begin{array}{c}
\text{C}_6\text{H}_5
\end{array} \rightarrow \text{Zn} + \text{NaOH}\]

(22)

\textsuperscript{92} T. Boehm and M. Grohwald, \textit{Arch. Pharm.} 274, 329 (1936).
\textsuperscript{94} L. Birkofer and H. Kachel, \textit{Naturwissenschaften} 41, 576 (1954).
\textsuperscript{96} L. Birkofer and R. Modic, \textit{Ann.} 604, 56 (1957).
\textsuperscript{97} E. Testa, L. Fontanella, and G. F. Cristiani, \textit{Farmaco (Pavia)}, \textit{Ed. sci.} 13, 437 (1958).
2,4-Dioxotetrahydro-1,3-oxazine derivatives (24) can be obtained by reacting β-hydroxy acids with sodium cyanate to form a urethane derivative (23) followed by the action of thionyl chloride.\textsuperscript{99-101}

\[
\begin{array}{c}
\text{R'}^,\text{COOH} \\
\text{R'}\text{CH}_2\text{OH}
\end{array} \xrightarrow{\text{NaOOCN}} \begin{array}{c}
\text{R'}^,\text{COOH} \\
\text{R'}\text{CH}_2\text{OC}=\text{O} \\
\text{NH}_2
\end{array}
\]

(23)

\[
\begin{array}{c}
\text{SOCl}_2
\end{array} \xrightarrow{\text{O}} \\
\begin{array}{c}
\text{R'} \\
\text{C}
\end{array} \begin{array}{c}
\text{NH} \\
\text{O}
\end{array} \text{O}
\]

(24)

2-Thionotetrahydro-1,3-oxazine derivatives (25) can be formed from dithiocarbamates by the action of carbon disulfide on 3-amino-propanol\textsuperscript{102,103}:

\[
\begin{array}{c}
\text{H}_2\text{C} \\
\text{H}_2\text{C} \text{OH}
\end{array} + \text{CS}_2 \xrightarrow{\text{(1) NaOH}} \xrightarrow{\text{(2) I}_2 \text{ in MeOH}} \text{NH} \xrightarrow{\text{or}} \begin{array}{c}
\text{O} \\
\text{S}
\end{array}
\]

(25)

The thiono derivatives of tetrahydro-1,3-oxazine became a subject matter of some interest since Kjaer and Jensen\textsuperscript{104} discovered that products of enzymatic hydrolysis of *Malcolmia maritima* contain 6-methyl- and 6,6-dimethyl-2-thionotetrahydro-1,3-oxazine (26). The authors proved the identity of these compounds with the products of cyclization of 3-hydroxypropyl-isothiocyanate in an alkaline medium.

\textsuperscript{102} U. S. Patent No. 2326732; *Chem. Abstr.* 38, 894 (1944).
By reacting phosphorous pentasulfide with dioxo derivatives of tetrahydro-1,3-oxazine, the oxygen atoms of both carbonyl groups are replaced by sulfur (27)\textsuperscript{105}:

\[
\begin{array}{c}
\text{P}_2\text{S}_5 \\
\xrightarrow{\text{H}_2\text{O}_2}
\end{array}
\]

The reaction is reversible and (24) can be recovered by the action of hydrogen peroxide.

C. Iminotetrahydro-1,3-oxazine Derivatives

Gabriel and Lauer first prepared a 2-iminotetrahydro-1,3-oxazine (28a) as early as 1890\textsuperscript{106} by reacting γ-bromopropylamine hydrobromide and potassium cyanate:

By tautomerism the product can also be regarded as a 5,6-dihydro-1,3-4\textit{H}-oxazine derivative (28b).

The same compound (28) can be prepared from an \textit{N}-guanyl or \textit{N}-nitroguanyl derivative of 3-aminopropanol.\textsuperscript{107} Also \textit{N}-(3-hydroxy-


propyl) derivatives of carbodiimide can be cyclized to yield 2-imino-tetrahydro-1,3-oxazine derivative (29).\textsuperscript{108}

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

(29)

Other derivatives of 3-aminopropanol and 3-halogenopropylamine can also be used to form 2-iminotetrahydro-1,3-oxazine derivatives.\textsuperscript{109-112} In some instances phenylisocyanate can be used as a cyclizing agent.\textsuperscript{90}

An interesting method of preparing 2-iminotetrahydro-1,3-oxazine derivatives (30) consists in cyclizing \(N\)-butyl-\(N\)-(\(\gamma\)-bromopropyl)-cyanamide.\textsuperscript{113}

**D. 5,6-Dihydro-1,3-4\(H\)-oxazines**

5,6-Dihydro-1,3-4\(H\)-oxazines (32) are among the best known 1,3-oxazines. Their preparation was first described by Gabriel and Elfeldt in 1891.\textsuperscript{111} The reaction consisted in benzylation of \(\gamma\)-bromopropylamine in the presence of sodium hydroxide by an intermediate formation of \(N\)-benzoyl-\(\gamma\)-bromopropylamine (31). The cyclization of the benzoyl derivative (31) occurred on simple heating, by prolonged keeping of a suspension of (31) in water,\textsuperscript{114} or by steam distillation.\textsuperscript{115-117}

A number of 2-aryl and 2-alkyl derivatives of 5,6-dihydro-1,3-4H-oxazine have been prepared in a similar way. An analogous reaction consists in thermal cyclization of \( N-(\gamma\text{-chloropropyl})-N'-\text{aryl} \) and \( N'-\text{alkyl} \) ureas.

5,6-Dihydro-1,3-4H-oxazines (33) can be formed from \( O\text{-acyl} \) derivatives of 3-propanolamine even where the formation of smaller rings would also have been possible, e.g.:

\[
\text{HOCH}_2\text{C}^\text{\NH}_3^\text{Cl}^- + \text{HC}\equiv\text{C}-\text{OR} \xrightarrow{\text{boiling with 20\% KOH}} \text{HOCH}_2\text{C}^\text{\NH}^\text{Br}^-\text{C}_{\text{C}_6\text{H}_5}\text{C}_{\text{C}_6\text{H}_5}
\]

A number of other reagents cyclize 3-propanolamines to 5,6-dihydro-1,3-4H-oxazines. These reagents are acetylenic ethers (which act as

\[
\text{H}_2\text{C}^\text{\NH}_2 + \text{HC}\equiv\text{C}-\text{OR} \xrightarrow{} \text{HOCH}_2\text{C}^\text{\NH}^\text{Br}^-\text{C}_{\text{C}_6\text{H}_5}\text{C}_{\text{C}_6\text{H}_5}
\]

---

a source of the acyl group) (34), esters of unsaturated acids, salts of amidines, and lactic acid esters. The last probably reacts through an intermediate formation of a lactamide [see also in following the formation of (38)].

A novel method of forming 2-aryl derivatives of 5,6-dihydro-1,3-4H-oxazine (35) consists in reacting 3-azidopropanol with aromatic aldehydes.

\[
\text{H}_2\text{C} = \text{C} \text{H}_2 \text{N}_3 + \text{ArCHO} \xrightarrow{\text{H}_2\text{SO}_4, 70-80^\circ} \text{Ar}
\]

Some rather unexpected formations of 5,6-dihydro-1,3-4H-oxazines have also been noted, e.g., reaction of γ-bromopropyl iminobenzoate with hydrogen sulfide, which yielded in addition to the main product (thiobenzoate) small amounts of (35):

\[
\text{H}_2\text{C} = \text{Br} \text{CH} \text{N} \text{Ar} \xrightarrow{\text{H}_2\text{S}} \text{Ar}
\]

1,3-Propanediol and its derivatives yield 5,6-dihydro-1,3-4H-oxazines (36) by reaction with nitriles in the presence of sulfuric acid.

\[
\text{H}_2\text{C} \text{C} = \text{CH}_3 + \text{CH}_3 \text{C} = \text{C} \text{H}_2 \text{OH} \xrightarrow{92\% \text{H}_2\text{SO}_4} \text{H}_3\text{C} \text{C} \text{CH}_3
\]

---

It was suggested that the reaction occurs via the formation of a carbonium ion (Scheme 1).

\[
\begin{align*}
\text{H}_3\text{C} \text{C} = \text{CH}_2 + \text{OSO}_3\text{H}^- & \rightarrow \text{H}_3\text{C} \text{C} = \text{CH}_2 \text{CH}_2\text{OH} \\
\text{H}_2\text{C} \text{C} = \text{CH}_2 + \text{CH}_2\text{CN} & \rightarrow \text{H}_3\text{C} \text{C} = \text{CH}_2 \text{N} = \text{C} - \text{OSO}_3\text{H} \\
\end{align*}
\]

**Scheme 1**

Meyers\textsuperscript{138} reported a new method of forming 5,6-dihydro-1,3-4H-oxazine derivatives (37) by reacting chloroolefins with nitriles in an acidic medium.

\[
\begin{align*}
\text{CH}_2\text{C} = \text{CH} = \text{CH}_2 & \rightarrow \text{CH}_3\text{C} = \text{CH} - \text{CH}_2\text{Cl} \\
\text{CH}_3\text{CH}_2\text{CN} & \rightarrow \text{CH}_3\text{C} = \text{CH} - \text{CH}_2\text{CH}_2\text{Cl} \\
\text{H}_2\text{SO}_4 & \rightarrow \text{CH}_3\text{C} = \text{CH} - \text{CH}_2\text{CH}_2\text{Cl} \\
\end{align*}
\]

(37)

Some amides can cyclize to form 5,6-dihydro-1,3-4H-oxazine derivatives as already mentioned.\textsuperscript{132} A rather complicated reaction of

\[
\begin{align*}
\text{CH}_2\text{C} = \text{CHCH}_2\text{CO}_2\text{Et} & \rightarrow \text{BrCH}_2\text{C} = \text{CHCH}_2\text{CO}_2\text{Et} \\
\text{CH}_3\text{CONHCO}_2\text{Et} & \rightarrow \text{H}_5\text{C}_2\text{OCOC}_2\text{H}_5 \\
\end{align*}
\]

(38)


this type (38) is the reaction of ethyl 2-allyl-2-acetamidomalonate with bromine, probably via the formation of an intermediate carbonium ion.

2-Thiol derivatives of 5,6-dihydro-1,3-4H-oxazine (e.g., 39) are formed by reacting carbon disulfide with 3-aminopropanols.\(^{102,139}\)

\[
\begin{align*}
\text{H}_3\text{C} & \text{C}^\text{C} \text{CH}_3 \\
\text{H}_2\text{C} & \text{C}^\text{C} \text{NH}_2 \\
\text{H}_3\text{C} & \text{H} \text{OH} \\
\text{CS}_2 & \xrightarrow{\text{KOH in ethanol}} \\
\text{H}_3\text{C} & \text{C}^\text{C} \text{CH}_3 \\
\text{H}_3\text{C} & \text{O} \text{SH} \\
\text{H}_3\text{C} & \text{C}^\text{C} \text{NH} \\
\text{H}_3\text{C} & \text{C}^\text{C} \text{SH} \\
\end{align*}
\]

\(\text{(39)}\)

E. OXO DERIVATIVES OF 5,6-DIHYDRO-1,3-4H-OXAZINE

Relatively little is known of this group of compounds. The only compound (40) with a keto group in the position 5 was prepared from hippuryl chloride and diazomethane\(^{10}\):

\[
\begin{align*}
\text{O} & \text{C} \text{C} \text{NH} \\
\text{Cl} & \text{O} \text{C} \text{C}_6\text{H}_5 \\
\text{H}_2\text{C} & \text{N} \text{C}_6\text{H}_5 \\
\text{H}_2\text{H} & \text{O} \text{C} \text{C}_6\text{H}_5 \\
\text{CH}_2\text{N}_2 & \xrightarrow{\text{CH}_2\text{N}_2} \\
\text{N} & \text{C}_6\text{H}_5 \\
\end{align*}
\]

\(\text{(40)}\)

\(\beta\)-Aminoacids are starting materials for the preparation of compounds (41) with oxo groups in the 6-position.\(^{140-142}\) The reaction described by Gosh\(^{140}\) can serve as an example:


\(^{140}\) T. N. Gosh, J. Indian Chem. Soc. 11, 23 (1934); Chem. Abstr. 28, 3736 (1934).


The only known derivative of this class was prepared from ethyl β-anilinecrotonate, ethyl acetoacetate, and benzaldehyde. In the first instance, a pyrimidine derivative is formed, this is then subjected to partial hydrolysis to form the 3,4-dihydro-1,3-2H-oxazine derivative (42).

4-Oxo derivatives (43 and 44) can be prepared from isothioureas and guanidines with diketene.

---

When an S-alkyl-\( N,N' \)-disubstituted isothiourea reacts with diketene in a boiling solvent,\(^{90,145}\) \( 2 \)-imino-4-keto-3,4-dihydro-1,3-\( 2H \)-oxazine derivatives (45) are formed. Analogous compounds can be prepared from dialkylcarbodiimides and diketene.\(^{146-148}\)

\[
\begin{align*}
\text{HN} & \quad \text{C}_6\text{H}_5 \\
\text{C} & \quad \text{NHC}_6\text{H}_5 \\
\text{\( \equiv \text{N} \)} & \quad \text{H}_3\text{C} \\
\text{\( \equiv \text{C} \equiv \text{O} \)} & \quad \text{NHC}_6\text{H}_5 \\
\text{(44)} & \quad \text{NH}_2
\end{align*}
\]

A 2,4-dioxo-3,4-dihydro-1,3-\( 2H \)-oxazine derivative (46) was formed\(^{149}\) by the thermal decomposition of ethyl 2-phenylcarbamoylmalonate:

\[
\begin{align*}
\text{O} & \quad \text{H}_3\text{C} \\
\text{\( \equiv \text{N} \)} & \quad \text{N} \quad \text{R}^1 \\
\text{\( \equiv \text{C} \equiv \text{O} \)} & \quad \text{N} \quad \text{R}^2 \\
\text{(45)} & \quad \text{C}_6\text{H}_5
\end{align*}
\]

H. 2,3-DIHYDRO-1,3-\( 6H \)-OXAZINES

This is the least investigated group of derivatives of 1,3-oxazine. Only oxo derivatives are known. Shapiro et al.\(^{150}\) obtained 2-oxo derivatives (47) by cyclizing ethynylalkyl arylcarbamates.

Another reaction leading to a 2,6-diketo derivative of 2,3-dihydro-1,3-6H-oxazine (48) consists in acting with sodium hypochlorite on maleic imide.\textsuperscript{127}

\begin{equation}
\text{HC-CO} \quad \text{NaOCl} \quad \text{HC-CO}
\end{equation}

I. 1,3-4H-Oxazines

The only known type of 1,3-oxazine containing two double bonds are the 4H-isomers.

The first example (49) was obtained by Wohl in 1901\textsuperscript{151} by reacting an aqueous solution of oxalic acid with the diethyl acetal of \(\gamma\)-benzoylaminoacetaldehyde.

\begin{equation}
(\text{COOH})_2
\end{equation}

General methods for the preparation of 1,3-4H-oxazines were given by Gabriel\textsuperscript{152} and Karrer and Miyamichi.\textsuperscript{153} They consist in reacting

\begin{equation}
\text{R}^3 \quad \text{R}^2 \quad \text{R}^3 \quad \text{R}^2 \quad \text{PCl}_3 \text{ or } \text{P}_2\text{O}_5
\end{equation}

\textsuperscript{127} A. Wohl, \textit{Ber. deut. chem. Ges.} \textbf{34}, 1914 (1901).

\textsuperscript{151} S. Gabriel, \textit{Ann.} \textbf{409}, 305 (1915).

1,3-oxazine derivatives

Phosphorous pentachloride and pentoxide, respectively, with \( \beta - (N\text{-acylamino}) \) derivatives of ketones and carboxylic acid esters.

However, the very existence of 1,3-4\( H \)-oxazines was questioned by Smith and Adkins.\(^{120} \) They claimed that no sufficient proof of the structure (50) exists. It appears that the problem requires further investigation.

IV. Chemical Properties

A. General

1,3-Oxazines are bases of varying strength and stability. Generally speaking, those which were derived by cyclization using aliphatic aldehydes are more stable than those formed from aromatic aldehydes.\(^{15,16} \)

1,3-Oxazines can form salts with strong acids. The salts vary with regard to their solubility and stability. Some of the hydrochlorides are hydrolyzed by water.\(^{44,154} \) Some less common salts are known, e.g., dichromates and ferrocyanates,\(^{106,114,118} \) chloroplatinates and chloroaurotates.\(^{11,22,114,118} \) Sometimes the picrates can also be used to identify the 1,3-oxazine derivatives.\(^{15,16,21-23,106,108,114,118,135} \) In some instances a special procedure is required to form the picrates, as the heterocyclic ring can open under the action of picric acid.\(^{154} \)

1. Tetrahydro-1,3-oxazines

The tetrahydro-1,3-oxazines which contain a free \( N \)-hydrogen atom can be \( N \)-acylated\(^{20,30,50,65,68,155} \) and \( N \)-nitrosated.\(^{14,21,26,60,80,156} \) Certain \( N \)-substituted derivatives of tetrahydro-1,3-oxazines can also react with acetic anhydride to form \( N \)-acetyl derivatives.\(^{20,67,157} \) Most tetrahydro-1,3-oxazines add methyl iodide to form quaternary salts.\(^{15,23,34,41,51,58,65,105} \)

A common feature of tetrahydro-1,3-oxazines is their ability to be hydrolyzed with ring opening. This occurs particularly readily in the presence of dilute mineral acids—preferably methanolic or ethanolic.\(^{26,27,58,108,159} \) The process can be much speeded up and the yield of

\(^{120} \) U. S. Patent No. 2905690; Chem. Abstr. 54, 11058 (1960).
\(^{154} \) M. Kohn, Monatsh. Chem. 25, 830 (1904).
\(^{120} \) U. S. Patent No. 2778826; Chem. Abstr. 51, 8809 (1957).
the open-chain compound increased under the influence of ultraviolet light.\textsuperscript{26,27,38,65}

Hydrolysis of 5-nitrotetrahydro-1,3-oxazines (51) to form 3-amino-2-nitropropanol derivatives (52) has been studied most extensively\textsuperscript{14,38-41,43,45,46,49,51,58,61}:

\[
\begin{align*}
\text{O}_2\text{N} \quad \text{R'} \quad \text{N} \quad \text{R}^+ & \quad \text{H}_2\text{O}^+ \quad \text{H}_2\text{O} \quad \text{O}_2\text{N} \quad \text{R'} \quad \text{N} \quad \text{R}^+ \quad \text{R}^+\text{CHO} \\
\text{R} \quad \text{C}=\text{O} \quad \text{OH} & \quad \text{OH} \\
(51) & \quad (52)
\end{align*}
\]

The reaction is reversible and (52) can be cyclized with aldehydes under neutral or mildly basic conditions.\textsuperscript{49}

The aldehyde $\text{R}''\text{CHO}$ liberated can be determined quantitatively by means of dinitrophenylhydrazone. In the case of formaldehyde ($\text{R}'' = \text{H}$) being split in an alcoholic-acid medium, it has been found that the formation of a dinitrophenylhydrazone is a relatively slow process. This seems to suggest that formaldehyde is originally split off in the form of an acetal which gradually yields formaldehyde under action of dinitrophenylhydrazone.

The opening the hetero ring along the bond $\text{O}—\text{C}$ (1-2 position) suggests this bond possesses the character of an acetal, or more exactly a hemiacetal. This was suggested by Urbański,\textsuperscript{4,150} and later confirmed by his colleagues with the help of infrared spectroscopy.\textsuperscript{62,135} Further proof of the hemiacetal character of the $\text{O}—\text{C}$ bond can be found in the catalytic reduction: ring opening occurs under the action of hydrogen on palladium or on nickel catalyst\textsuperscript{64,120,161,162} and reduction with sodium amalgam\textsuperscript{163} or with lithium-aluminum hydride.\textsuperscript{165}

If the acid hydrolysis of 1,3-oxazine derivatives is followed by acting with phenyl-isothiocyanate, thiourea derivatives can be formed.\textsuperscript{164}

2-Oxotetrahydro-1,3-oxazine derivatives of type (53) can be hy-

\textsuperscript{100} T. Urbański, \textit{Roczniiki Chem.} 25, 257 (1951).
\textsuperscript{103} W. Stühmer and W. Heinrich, \textit{Chem. Ber.} 84, 224 (1951).
drolyzed to form unsaturated ketones as result of more profound changes in the heterocyclic ring\(^\text{77}\):

\[
\text{\begin{align*}
\text{HO} & \quad \text{\begin{align*}
\text{Cl}_3\text{C} & \quad \text{R} \\
\text{Cl}_3\text{C} & \quad \text{O} \\
\text{NH} &
\end{align*}} \\
\text{\begin{align*}
\rightarrow \quad \text{Cl}_3\text{C} & \quad \text{\begin{align*}
\text{CH} = \text{CH} & \quad \text{CO} & \quad \text{R}
\end{align*}}
\end{align*}}
\]

(53)

Ring opening of some derivatives of tetrahydro-1,3-oxazine can also occur when warmed with aqueous sodium hydroxide\(^\text{113}\):

\[
\text{\begin{align*}
\text{\begin{align*}
\text{N} & \quad \text{\begin{align*}
\text{C}_4\text{H}_9 & \quad \text{OH} \\
\text{O} & \quad \text{\begin{align*}
\text{\begin{align*}
\rightarrow \quad \text{\begin{align*}
\text{C}_4\text{H}_9\text{NHCH}_2\text{CH}_2\text{CH}_2\text{OH} \\
\text{20\% NaOH} & \quad \text{2 hr}
\end{align*}}
\end{align*}}
\end{align*}}
\end{align*}}
\end{align*}}
\]

The simple ring opening of tetrahydro-1,3-oxazine derivatives is not the only possible reaction of these heterocyclic compounds catalyzed by mineral acids. An interesting rearrangement of 6-aryl-6-alkyltetrahydro-1,3-oxazines when warmed with concentrated hydrochloric acid was found by Schmiedle and Mansfield\(^\text{67,157,165}\):

\[
\text{\begin{align*}
\text{\begin{align*}
\text{\begin{align*}
\text{\begin{align*}
\text{\begin{align*}
\text{CH}_3 & \quad \text{Ar} \\
\text{N} & \quad \text{R}
\end{align*}}
\end{align*}}
\end{align*}}
\end{align*}}
\]

This reaction yields derivatives of 1-alkyl-4-aryl-4-piperidinol\(^\text{65,158,166-169}\).

In a basic medium, 5-nitro-5-hydroxymethyltetrahydro-1,3-oxazine derivatives can be coupled with aryl diazonium salts to form arylazo derivatives (54) with the elimination of a molecule of formaldehyde\(^\text{170}\).


2. 5,6-Dihydro-1,3-4H-oxazines

Gabriel has demonstrated the instability of 5,6-dihydro-1,3-4H-oxazines by reacting the hydrobromide of 2-phenyl-5,6-dihydro-1,3-4H-oxazine (55) with water. Ring opening occurs with the formation of 3-aminopropylbenzoate which is rearranged into 3-benzamidopropanol.

A formation of 5,6-dihydro-1,3-4H-oxazine derivatives from 3-acetylaminopropanol derivatives has also been described (Scheme 2).

Further examination of the properties of 5,6-dihydro-1,3-4H-oxazine derivatives has shown that the ring opening is acid catalyzed. Alkaline hydrolysis with 10% NaOH leading to ring opening was also described. The nature of the ring opening is much influenced by the substituents.

3. 3,4-Dihydro-1,3-2H-oxazines

2-Imino derivatives of 4-oxo-3,4-dihydro-1,3-2H-oxazines (56) are hydrolyzed with dilute hydrochloric acid to the corresponding 2,4-
1,3-OXAZINE DERIVATIVES

Dioxo oxazines (57). The dioxo (57) when warmed with amines is transformed into dioxo-1,2,3,4-tetrahydropyrimidine derivatives (58).

\[
\text{(56)} \quad \overset{\text{H}_3\text{O}^+}{\longrightarrow} \quad \text{(57)}
\]

\[
\text{(58)}
\]

4. 1,3-4H-Oxazines

1,3-4H-Oxazines (59) are also susceptible to hydrolysis by water, particularly in the presence of acids, e.g.,

\[
\text{(59)} \quad \overset{\text{H}_2\text{O}}{\longrightarrow} \quad \overset{\text{HCl}}{\longrightarrow} \quad \overset{\text{OH}^-}{\longrightarrow}
\]

A noteworthy feature of this sequence of reactions is the O→N migration of the acyl group and the final stabilization as the N-acylaminoketone.

B. CHEMICAL STRUCTURE

Although all the syntheses of 1,3-oxazine derivatives and their chemical properties left little doubt as to their chemical constitution,
there was until recently a need for further physicochemical evidence to confirm the structure. This was particularly required as some of the early physicochemical evidence did not fully agree with the structural formulas. Thus, the molecular refraction calculated for 1,3-oxazine derivatives was lower than found experimentally.\textsuperscript{20,62} The depression $\Delta M_D$ was found to be 0.4–0.9 for 5-nitro derivatives of tetrahydro-1,3-oxazine.

Ultraviolet absorption spectra of tetrahydro-1,3-oxazines do not show any maximum.\textsuperscript{26} Only after the introduction of a chromophoric group do bands appear. Thus 5-nitro derivatives show a strong maximum near 270 m$\mu$, which is typical for a nitro group,\textsuperscript{40,160,172–175} and another one near 200 m$\mu$ which is probably also produced by the nitro group.\textsuperscript{40,160,172–175} In the instance of 5-nitro-5-hydroxymethyl derivatives, the absorption is much weakened; this was explained by Urbański\textsuperscript{172} in terms of a hydrogen bond between the hydroxyl and the nitro group. Other chromophores, such as C=O, C=NH, C=C, also cause the appearance of absorption maxima in the range 210–265 m$\mu$ and near 360 m$\mu$.

Infrared absorption spectra gave more information regarding the structure of 1,3-oxazine derivatives. These studies were mainly concerned with tetrahydro-1,3-oxazine\textsuperscript{20,49,62,80,87,105,176} and dihydro-1,3-oxazine derivatives.\textsuperscript{62,86,135,137,147,177} According to Eckstein et al.\textsuperscript{62} a number of bands of frequencies 1150–1050, 955–925, and 855–800 cm$^{-1}$ characterize the hemiacetal bond C—O—C. Lukeš et al.\textsuperscript{178} expressed the view that a triplet of bands at 1143, 1129, and 1083 cm$^{-1}$ characterized the tetrahydro-1,3-oxazine ring. However, Bergmann and Kaluszyner\textsuperscript{20} assigned these bands to the N—C—O system in the tetrahydro-1,3-oxazines.

Other functional groups in tetrahydro-1,3-oxazine derivatives, such as NO$_2$,\textsuperscript{62} CO,\textsuperscript{80,87,105} NH (amines),\textsuperscript{62} and NH (amides),\textsuperscript{80,87,105} give bands whose frequencies are within the generally accepted ranges.

In the case of 5,6-dihydro-1,3-4H-oxazine derivatives, the infrared

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\textsuperscript{172} T. Urbański, \textit{Bull. acad. polon. sci., Classe III} 1, 239 (1953).
\textsuperscript{175} T. Urbański, \textit{Roczniki Chem.} 33, 635 (1959).
spectra confirmed their structure. A number of papers was also concerned with elucidating the influence of substituents in the 2-position on the C=N stretching frequency which usually has a value near 1650 cm$^{-1}$. The lowest frequency (1608 cm$^{-1}$) was recorded when the vinyl group was in the 2-position. Wrong interpretation of some results was corrected by Meyers.

The infrared spectra of 2,4-dioxo and 2-imino-4-oxo-3,4-dihydro-1,3-4$H$-oxazines were also examined and found to confirm their structural formulas. An interesting result here was that the $\nu$C=N of the side imino group and the $\nu$C=C in the ring have the frequencies 1594-1590 cm$^{-1}$ and 1693-1670 cm$^{-1}$, respectively.

C. Conformation

Lukeš et al. discussed the formation and hydrolysis of tetrahydro-1,3-oxazine derivatives and came to the conclusion that tetrahydro-1,3-oxazine derivatives existed in a chair form similar to that of cyclohexanes. Gürire and Urbański came to the same conclusion on the evidence of measured and calculated dipole moments of 5-nitro-5-alkyl-3-cyclohexyltetrahydro-1,3-oxazines. They found that the 5-nitro group is always axial even when the 5-alkyl group is as small as methyl.

Drefahl and Hörhold discussed the mechanism of N$\rightarrow$O acyl migration in N-benzoyl-1,2-diphenyl-3-aminopropanols. The migration does not seem to be possible in the erythro isomer as it would give an intermediate tetrahydro-1,3-oxazine with a bulky phenyl group in axial position. Consequently the erythro isomer is cyclized with inversion to form 2,5,6-triphenyl-5,6-dihydro-1,3-4$H$-oxazine.

---

Thus a semichair conformation with equatorial phenyl groups is formed.

Similarly in epimeric transformation of N-acyl derivatives of 1,3-diphenyl-3-aminopropanol, the formation was accepted\textsuperscript{181} of 5,6-dihydro-1,3-4$H$-oxazines with a conformation similar to (61).

Stereospecificity was also shown in the reductive aminomethylation\textsuperscript{182} of 3-aminopropanol derivatives by the Eschweiler-Clark method. Threo-3-methyl-5,6-diphenyl- (62) and erythro-3-methyl-4,6-diphenyltetrahydro-1,3-oxazine (63) were formed as shown, but if starting materials of the opposite configuration were used, then only the corresponding dimethylamino derivatives were formed, and ring closure did not occur.

The formation of various tetrahydro-1,3-oxazine derivatives was used to separate diastereo isomers of 3-amino-1,3-diphenylpropanol.


D. Possible Practical Applications

1. Theoretical Organic Chemistry

The ability of compounds containing NH and OH (cis) groups in the positions 1 and 3 to each other to form a 1,3-oxazine ring can be used to establish the absolute configuration of the corresponding structural fragments in some alkaloids. The method suggested by Hardegger and Ott154 consisted in forming 1,3-oxazine rings by acting with aldehydes in anhydrous medium. A number of alkaloids were investigated in this manner.12,17,143,144,154,176,178,179,183–186

As previously mentioned, N → O acyl migration in derivatives of 3-aminopropanol was proved to occur via the formation of a 1,3-oxazine intermediate.11,12,13,180,182,187,188

2. Biologically Active Compounds

A number of drugs with a 1,3-oxazine ring have been suggested in connection with chemical work in the field. Lately such interest has increased since a natural product—geissospermine—was found to contain this ring.169 However, the work in this field is still experimental, based on working hypotheses.

Tetrahydro-1,3-oxazine derivatives were suggested as analgesics and anticonvulsants190 or analgesics and antipyretics.88,89,191 Mono- and dioxo-1,3-oxazine derivatives related to cyclic urethanes were suggested as depressants of the nervous system,195,128 and sedatives.192 2-Thiono-4-oxo derivatives were also suggested as anticonvulsants and sleeping drugs.191 Wider experiments on the chemotherapeutic activity of 1,3-oxazine derivatives were carried out by Urbański et al. They were originally concerned with antitubercular activity,1,2,3,37,38,40 then with other bacteria and viruses,1,26,27,193 and eventually with oncostatic

187 N. L. Wendler, Experientia 9, 416 (1953).
192 R. Fusco and E. Testa, Farmaco (Pavia), Ed. sci. 12, 823 (1957); Chem. Abstr. 52, 11853 (1958).
activity.\textsuperscript{9,53,69,194} The latter seem to have prospects for practical application.

According to Urbański et al.\textsuperscript{9} biological activity of 1,3-oxazine derivatives is due to the active CH\textsubscript{2} group in the 2-position. The use of tetrahydro-1,3-oxazines was also suggested against some infections in veterinary service.\textsuperscript{63,195} The suggested use of tetrahydro-1,3-oxazines as herbicides\textsuperscript{28,61} did not seem to be a success.

Dihydro-1,3-oxazines have been suggested as analgesics,\textsuperscript{119} sedatives and spasmylytics,\textsuperscript{11} and fungicides.\textsuperscript{125,128,135}

Another line of approach to the practical application of 1,3-oxazine derivatives was the suggested use of tetrahydro-1,3-oxazine derivatives as detergents for textile industry,\textsuperscript{82} as anticorrosion chemicals,\textsuperscript{191,195} and polymers from 2-oxo derivatives as additives to improve the properties of paper and textiles.\textsuperscript{132,196,197}

Both tetrahydro- and dihydro-1,3-oxazine derivatives have been suggested as passive components of azo dyes.\textsuperscript{198,199}

\textsuperscript{193} D. Rożniecka, Med. Doświadczalna i Mikrobiol. 3, 149 (1951); Chem. Abstr. 46, 4675 (1952).
\textsuperscript{196} U. S. Patent No. 2806017; Chem. Abstr. 52, 792 (1958).
\textsuperscript{199} U. S. Patent No. 2873268; Chem. Abstr. 54, 2757 (1960).