OXAZOLINES. THEIR PREPARATION, REACTIONS, AND APPLICATIONS

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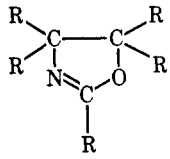
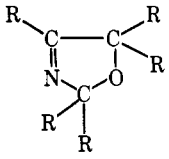
Contents

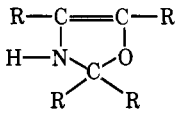
I. Introduction

Oxazolines have been known for many years,[1] but only in recent years has the chemical literature shown considerable activity in this field. An excellent review article[2] was published in 1949 covering the chemistry of oxazolines to that time. The literature following publication of that article indicates a many-fold increase in university and commercial activity involving preparation, reactions, and uses of oxazolines. The work reported during that 20-year period is the subject for this article.

Oxazolines are five-membered heterocyclic compounds having one double bond. The double bond may be located in one of three positions, therefore making possible the existence of three different oxazoline rings. The 2-oxazoline structure is the most common, with 3-oxazolines and 4-oxazolines existing primarily as laboratory research compounds.


2-oxazoline


3-oxazoline


4-oxazoline

There are many ways in which oxazolines may be formed, as indicated in the section on preparation. Commercially, the main interest has been in 2-oxazolines derived from amino alcohols and low-cost carboxylic acids. The amino alcohols of interest are those having an amino group and a hydroxyl group on adjacent carbon atoms. Those of greatest interest are ones having complete substitution on the carbon atom to which the amino group is attached. The substituted amino alcohols cyclize readily when heated with carboxylic acids to give high yields to 2-oxazolines. Unsubstituted amino alcohols form amides but cyclize only with difficulty. Some of

(1) R. Andreasch, *Monatsh. Chem.*, **5**, 33 (1884).
(2) R. H. Wiley and L. L. Bennett, Jr., *Chem. Rev.*, **44**, 447 (1949).

the lower molecular weight amides can be distilled without cyclizing.

When amino alcohols having complete substitution on the carbon atom to which the amino group is attached became commercially available, a noticeable acceleration in oxazoline research took place. Those of particular interest were 2-amino-2-methyl-1-propanol, 2-amino-2-methyl-1,3-propanediol, 2-amino-2-ethyl-1,3-propanediol, and 2-amino-2-hydroxymethyl-1,3-propanediol.

The oxazoline ring presents an interesting structure on which to build a wide variety of compounds having properties which make them of interest in many fields of application. Hydrogens located on the α carbon of an alkyl group in the 2 position are active and are readily replaced with other groups. In addition, the 2-oxazoline ring has two sites in the 4 position and two in the 5 position where reactive groups may be located. Also, the nitrogen of the oxazoline is basic and forms salts with acids and quaternary compounds with alkyl halides. The functionality of oxazolines, the wide variety of derivatives they offer, and their versatility in application are illustrated throughout this review.

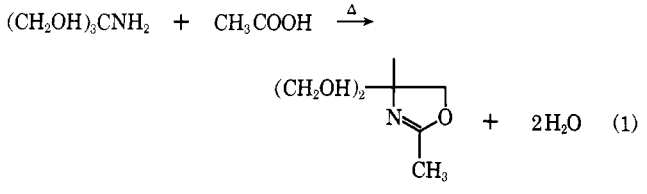
Contributions to the development of oxazoline chemistry have been worldwide and generous during the period covered by this review, from 1949 to the end of 1969. It is intended that published work pertinent to the advancement of oxazoline chemistry will be included in this article.

II. Preparation of Oxazolines

A. FROM AMINO ALCOHOLS

Oxazolines are prepared in various ways using amino alcohols. Usually the simplest and most inexpensive process involves the reaction of an amino alcohol with a carboxylic acid. The amino alcohol must have the NH_2 and OH groups on adjoining carbon atoms, and the acid may be aliphatic or aromatic. When the amino alcohol is completely substituted on the carbon containing the NH_2 group, the reaction with an acid proceeds smoothly through the amide to the oxazoline with elimination of water.

Refluxing 2-amino-2-hydroxymethyl-1,3-propanediol in acetic acid until the theoretical water of reaction is removed gives 2-methyl-4,4-bis(hydroxymethyl)-2-oxazoline in high yield. The reaction is illustrated by the following equation.

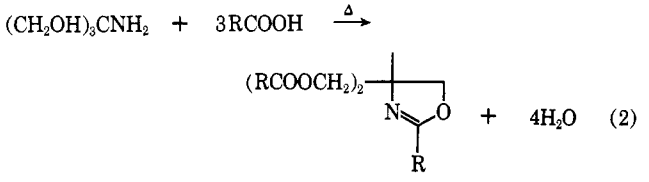


(1)

Reaction with an aromatic acid, such as benzoic acid, gives an oxazoline having phenyl substitution in the 2 position. For example, 2-phenyl-4,4-bis(hydroxymethyl)-2-oxazoline can be obtained from the reaction of 2-amino-2-hydroxymethyl-1,3-propanediol and benzoic acid by refluxing the mixture for 18 hr and removing water as a xylene azeotrope.[3]

The same product has been prepared by heating the amino alcohol and benzoic acid to 170° *in vacuo* to remove water, instead of the more common procedure of using an azeotropic agent. This is claimed to reduce the reaction time to less than 12 hr.[4]

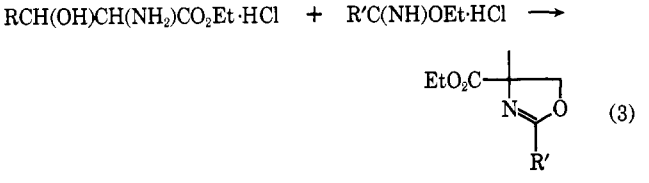
Oxazoline esters or diesters are also formed if the amino alcohol has more than one hydroxyl group available for reaction. Acyloxymethyloxazolines have been prepared in high yield from treating 2 mol of an organic acid with an α,β-aminodiol at about 150–240° for about 10 hr using benzene as an azeotrope to remove water. 2-Heptyl-4-methyl-4-octanoyloxymethyl-2-oxazoline is obtained from octanoic acid and 2-amino-2-methyl-1,3-propanediol. The oxazoline diester is formed when the amino alcohol is 2-amino-2-hydroxymethyl-1,3-propanediol.[5]



(2)

Methyl esters are also suitable for preparing oxazolines from amino alcohols. Methyl salicylate and 2-amino-2-hydroxymethyl-1,3-propanediol heated for 1 hr at 180–190° and then kept 2 hr at the same temperature at 0.5 mm gives 2-(2-hydroxyphenyl)-4,4-bis(hydroxymethyl)-2-oxazoline. Other oxazolines have been reported where the substituent in the 2 position was 4-hydroxyphenyl, 3-chlorophenyl, 2-chlorophenyl, 3,4,5-trimethoxyphenyl, 3-hydroxyphenyl, 4-methoxyphenyl, α-naphthyl, and 3-nitrophenyl.[6]

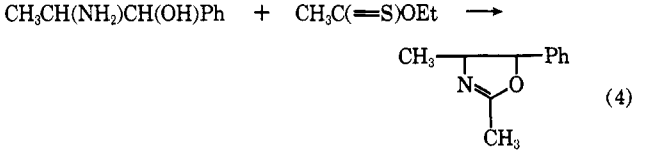
Also, amino alcohols have been treated with an imidic acid ester to obtain 2-oxazolines as illustrated by eq 3.



(3)

Products prepared by this reaction include 2-methyl-5-phenyl-4-hydroxymethyl-2-oxazoline, 2-methyl-5-phenyl-4-acetoyloxymethyl-2-oxazoline, 2-methyl-5-(*p*-nitrophenyl)-4-hydroxymethyl-2-oxazoline, and 2-dichloromethyl-5-phenyl-4-acetoyloxymethyl-2-oxazoline.[7,8]

Ethyl thionacetate will react with amino alcohols to give 2-oxazolines. For example, ethyl thionacetate can be heated with 2-amino-1-phenyl-1-propanol to give 2,4-dimethyl-5-phenyl-2-oxazoline.[9]



(4)

(3) J. H. Billman and E. E. Parker, U. S. Patent 2,556,791 (1951); *Chem. Abstr.*, **46**, 525 (1952).

(4) V. Rosnati and D. Misiti, *Rend. Ist. Super. Sanita*, **23**, 603 (1960); *Chem. Abstr.*, **55**, 5463 (1961).

(5) P. F. Tryon, U. S. Patent 2,504,951 (1950); *Chem. Abstr.*, **44**, 6887 (1950).

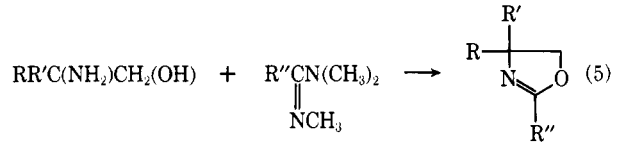
(6) L. F. Wiggins, C. C. Beard, and J. W. James, British Patent 953,427 (1964); *Chem. Abstr.*, **60**, 15875 (1964).

(7) Parke, Davis and Co., British Patent 704,946 (1954); *Chem. Abstr.*, **49**, 10370 (1955).

(8) G. W. Moersch, U. S. Patent 2,562,113 (1951); *Chem. Abstr.*, **46**, 3080 (1952).

(9) P. Kornmann and A. Funke, *C. R. Acad. Sci.*, **240**, 321 (1955); *Chem. Abstr.*, **50**, 1774 (1956).

Some 2-oxazolines have been prepared from amidine salts and amino alcohols. The general reaction conditions include heating the amidine salt and amino alcohol at about 140° for up to 4 hr.



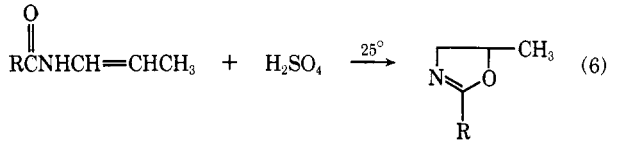
2-(*p*-Methylsulfonylphenyl)-2-oxazoline can be prepared from 2-amino-1-ethanol and *N*-phenyl-*p*-(methylsulfonyl)-benzamidine benzenesulfonate.[10,11]

2-Substituted-2-oxazolines have been prepared by the reaction of an organic trihalide with an amino alcohol in the presence of Na_2CO_3. 2-Phenyl-2-oxazoline is obtained from the reaction of trichloromethylbenzene and 2-amino-1-ethanol; 1,1,1-trichloroethane and the same amino alcohol give 2-methyl-2-oxazoline. Good yields are obtained by this method.[12]

B. FROM AMIDES

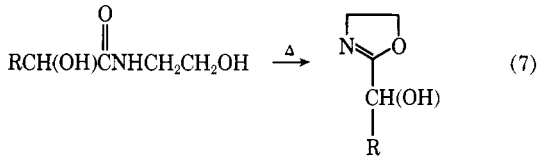
A considerable volume of work has been reported where oxazolines are prepared from amides. Some amides cyclize with difficulty, requiring the presence of a dehydrating agent and the use of high temperatures. Others go to the oxazoline with only moderate heat and in the absence of dehydrating agents.

The preparation of 2-substituted-5-methyl-2-oxazolines has been accomplished by treating *N*-(allyl)amides with concentrated H_2SO_4 at below 25° (eq 6). The addition of 96%



H_2SO_4 to *N*-allyl-*p*-toluamide gives 2-(*p*-tolyl)-5-methyl-2-oxazoline in 50% yield.[13]

The reaction of an α-hydroxy acid with an amino alcohol gives an *N*-(2-hydroxyethyl)hydroxyamide, which can be converted to a 2-(1-hydroxyalkyl)-2-oxazoline by heating to about 280° at 3–4 mm in a reactor filled with kaolin.[14]

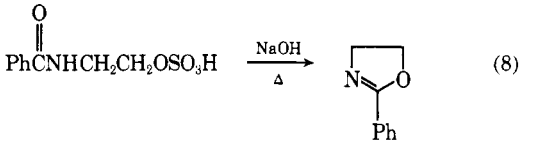


Low yields of 2-oxazoline have been obtained by heating *N*-(2-hydroxyethyl)formamide to 150–300° at reduced pressure in the presence of a dehydrating agent such as Al_2O_3.[15]

Improved yields are obtained by heating *N*-(2-hydroxyethyl)amides to 275° at 200 mm in a reactor filled with $Na_2B_4O_7$. The dehydration of *N*-(2-hydroxyethyl)caproamide gives 2-pentyl-2-oxazoline.[16]

Al_2O_3-catalyzed dehydration in the gaseous phase has been used to convert *N*-(2-hydroxyethyl)amides to 2-substituted-2-oxazolines. For example, *N*-(2-hydroxyethyl)butyramide dropped onto Al_2O_3 in a quartz tube at 600° gives 2-propyl-2-oxazoline.[17-21]

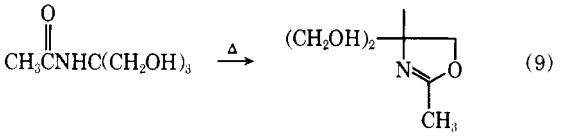
The sodium salt of *N*-benzoyl-2-aminoethyl sulfate in aqueous NaOH is converted in 70% yield to 2-phenyl-2-oxazoline when heated at boiling for only 15 min.[22]



The attempted tosylation of *N*-aroyl derivatives of 2 amino-2-methyl-1-propanol has given good yields of the corresponding 2-aryl-4,4-dimethyl-2-oxazoline. When aryl is phenyl a yield of 74% to the amide and 74% from amide to oxazoline has been reported.[23]

The reaction of acetic anhydride with 2-amino-1-phenyl-1-propanol gives an amide mixture which can be treated with H_2SO_4 and neutralized with K_2CO_3 to give 2,4-dimethyl-5-phenyl-2-oxazoline.[24]

Conversion of alkanolamides to oxazolines has been accomplished by heating in the absence of dehydrating agents to temperatures above 200°. High-boiling solvents such as toluene or xylene are used to aid in removing water of reaction. 2-Methyl-4,4-bis(hydroxymethyl)-2-oxazoline is obtained by heating the amide from 2-amino-2-hydroxymethyl-1,3-propanediol and acetic anhydride until theoretical water is removed.[25]



Monoethanolamides of several fatty acids have been prepared by refluxing the reactants for about 5 hr at about 150°. The amides can be converted to 2-alkyl-2-oxazoline hydrochloride by treatment with $SOCl_2$ at room temperature.[26]

(10) P. Oxley and W. F. Short, British Patent 615,006 (1948); *Chem. Abstr.*, **43**, 7512 (1949).

(11) P. Oxley and W. F. Short, *J. Chem. Soc.*, 1100 (1950); *Chem. Abstr.*, **44**, 10702 (1950).

(12) A. J. Levy and M. H. Litt, U. S. Patent 3,402,178 (1968); *Chem. Abstr.*, **69**, 96750 (1968).

(13) S. P. McManus, J. T. Carroll, P. M. Grohse, and C. V. Pittman, *Org. Prep. Proced.*, **1**, 183 (1969); *Chem. Abstr.*, **71**, 70525 (1969).

(14) A. J. Levy and M. H. Litt, French Patent 1,546,405 (1968); *Chem. Abstr.*, **71**, 50827 (1969).

(15) L. G. Hess, British Patent 758,972 (1956); *Chem. Abstr.*, **51**, 11390 (1957).

(16) A. A. Eisenbraun, U. S. Patent 3,312,714 (1967); *Chem. Abstr.*, **67** 82206 (1967).

(17) Chemische Werke Huels A.-G., French Patent 1,436,298 (1966); *Chem. Abstr.*, **65**, 20129 (1966).

(18) Chemische Werke Huels A.-G., French Patent 1,436,297 (1966); *Chem. Abstr.*, **66**, 18705 (1967).

(19) W. Seeliger, E. Aufderhaar, W. Diepers, R. Feinauer, R. Nehring, W. Thier, and H. Hellmann, *Angew. Chem.*, **78** (20), 913 (1966); *Angew. Chem., Int. Ed. Engl.*, **5** (10), 875 (1966); *Chem. Abstr.*, **66**, 94973 (1967).

(20) M. H. Litt and A. J. Levy, Belgian Patent 666,829 (1965); *Chem. Abstr.*, **66**, 2574 (1967).

(21) W. Seeliger and W. Thier, *Justus Liebigs Ann. Chem.*, **698**, 158 (1966); *Chem. Abstr.*, **66**, 37856 (1967).

(22) A. Jager and L. Orthner, German Patent 955,951 (1957); *Chem. Abstr.*, **53**, 16152 (1959).

(23) R. N. Boyd and R. H. Hansen, *J. Amer. Chem. Soc.*, **75**, 5896 (1953).

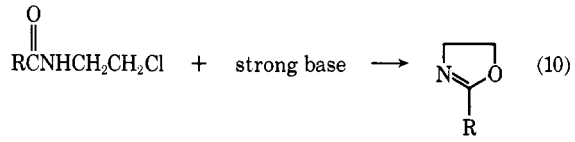
(24) T. Taguchi and M. Kojima, *J. Pharm. Soc. Jap.*, **74**, 1293 (1954); *Chem. Abstr.*, **49**, 15862 (1955).

(25) E. I. Valco, U. S. Patent 2,416,552 (1947); *Chem. Abstr.*, **41**, 3823 (1947).

(26) Y. Ishii, M. Mase, and A. Kaneshiro, *Yukagaku*, **7**, 70 (1958); *Chem. Abstr.*, **55**, 5993 (1961).

C. FROM HALOAMIDES

Haloamides are converted readily to oxazolines by a strong base and rather slowly by weak base (eq 10). Preparation of



(10)

N-(2-halo-1-ethyl)amides in good yield can be accomplished by mixing the halo alcohol or halo olefin with a nitrile at 35° for 3 hr and then adding Na_2CO_3.[27] The rate of reaction of *N*-(2-bromoethyl)benzamides with methoxide ion to form 2-oxazolines has been reported.[28,29]

The reaction of *N*-(2-bromoethyl)phthalimide with warm 30% KOH solution gives about 75% yield to 2-(*o*-carboxyphenyl)-2-oxazoline.[30]

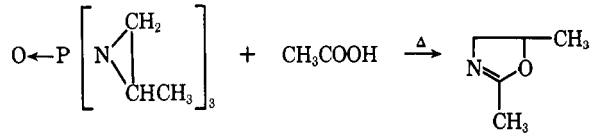
The addition of *N*-(2-chloroethyl)acetamide to a refluxing suspension of NaOH in hexane gives 50% yield to 2-methyl-2-oxazoline.[31,32] A yield of 99% to crude 2-methyl-2-oxazoline is obtained when *N*-(2-chloroethyl)acetamide and anhydrous Na_2CO_3 are mixed and heated to 65° under reduced pressure (30–55 mm).[33–35]

N-Aroyl-2-bromoethylamines react with strongly basic amines to give oxazolines and amine hydrobromides, and with weakly basic amines (such as aromatic amines or the salts) to give HBr salts of *N*-aroyl-*N'*-aryl-substituted diamines. For example, *N*-(2-bromoethyl)benzamide gives 2-phenyl-2-oxazoline in good yields when treated with strong bases (100% with sodium ethoxide). Acceptors in the *N*-aroyl compound accelerate oxazoline formation. *p*-Nitrophenyl-2-oxazoline forms eight times as fast as phenyl-2-oxazoline.[36,37]

When *N*-(2-bromoethyl)benzamide and diethylamine are boiled in benzene, 2-phenyl-2-oxazoline is formed.[38] Similarly, 2-phenyl-2-oxazoline can be obtained by heating to 50° an ethanolic NaOH solution containing *N*-(2-bromoethyl)-benzamide.[39]

D. FROM AZIRIDINES

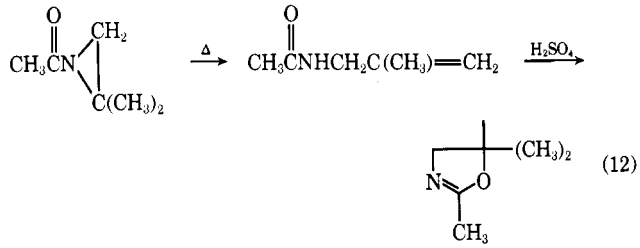
The rate of reaction of acetic acid with tris(2-methyl-1-aziridinyl)phosphine oxide in dioxane and in toluene to give 2,5-dimethyl-2-oxazoline has been investigated at 60 to 100°. The rate is third order to about 50% reaction, then deviates rapidly.[40]



(11)

Refluxing suitable organic acids and aziridinylphosphine oxide in toluene gives mixtures which can be thermally decomposed to give 2-substituted oxazolines. For example, tris[1-(2-phenyl)aziridinyl]phosphine oxide in toluene refluxed with butyric acid for 9 hr gives a mixture of 2-propyl-5-phenyl-2-oxazoline and 2-propyl-4-phenyl-2-oxazoline.[41,42]

Pyrolytic rearrangement of 1-acyl-2,2-dimethylethylenimine gives high yields of the *N*-(methallyl)amide, which can be converted to 2-oxazolines by mixing with H_2SO_4 at 30–40° and neutralizing with NaOH. 2,5,5-Trimethyl-2-oxazoline is obtained from 1-acetyl-2,2-dimethylethylenimine.[43]



(12)

Pyrolysis of *N*-(*p*-nitrobenzoyl)cyclooctenimine in toluene gives *cis*-*N*-(*p*-nitrobenzoyl)-3-cyclooctenylamine and 4,5-hexamethylene-2-(*p*-nitrophenyl)-2-oxazoline. 1-(*p*-Nitrobenzoyl)-2-benzylaziridine refluxed in toluene forms *N*-(*trans*-cinnamyl)-*p*-nitrobenzamide in good yield, which can be converted to 2-(*p*-nitrophenyl)-5-benzyl-2-oxazoline by treatment with H_2SO_4.[44]

Catalytic rearrangement of *N*-acylethylenimines using $SnCl_4$ gives fair yields to 2-substituted-2-oxazolines. For example, *N*-acetylethylenimine heated 40 hr under a nitrogen blanket in a sealed tube at 70° gives 2-methyl-2-oxazoline.[45]

Isomerization of 1,1'-carbonylbisaziridines with catalytic amounts of $Bu_4N^+I^-$ gives 2-aziridino-2-oxazolines.[46] Isomerization of *N*-*p*-ethoxybenzoylethylenimine in refluxing heptane in the presence of small amounts of $AlBr_3$ or $AlCl_3$ or 2-bromoethylamine hydrobromide gives 2-(*p*-ethoxyphenyl)-2-oxazoline.[47]

Heating aziridines with an alkali metal iodide at 50–150° in a solvent gives the corresponding 2-oxazoline by molecular rearrangement. Specifically, ethyl-1-aziridinyl formate with

(27) R. M. Lusskin and J. J. Ritter, *J. Amer. Chem. Soc.*, **72**, 5577 (1950).
(28) H. W. Heine, *ibid.*, **78**, 3708 (1956).
(29) H. W. Heine, *ibid.*, **79**, 907 (1957).
(30) K. Kormendy and J. Volford, *Acta Chim. Acad. Sci. Hung.*, **32**, 115 (1962); *Chem. Abstr.*, **58**, 1392 (1963).
(31) S. S. Skorokhodov, S. G. Ershova, N. V. Mikhailova, and A. A. Vansheidt, *Zh. Obshch. Khim.*, **31**, 3626 (1961); *Chem. Abstr.*, **57**, 8555 (1962).
(32) A. A. Vansheidt, S. S. Skorokhodov, S. G. Ershova, and N. V. Mikhailova, *Vysokomol. Soedin.*, **3**, 320 (1961); *Chem. Abstr.*, **61**, 3084 (1964).
(33) Allied Chemical Corp., Netherlands Appl. 6,605,339 (1966); *Chem. Abstr.*, **66**, 37911 (1967).
(34) T. G. Bassiri, French Patent 1,477,049 (1967); *Chem. Abstr.*, **68**, 21924 (1968).
(35) A. J. Levy and M. H. Litt, French Patent 1,560,117 (1969); *Chem. Abstr.*, **71**, 82070 (1969).
(36) K. Kormendy and J. Volford, *Acta Chim. Acad. Sci. Hung.*, **32**, 121 (1962); *Chem. Abstr.*, **58**, 1444 (1963).
(37) K. Kormendy, P. Sohar, and J. Volford, *Ann. Univ. Sci. Budapest. Rolando Eotvos Nominatae, Sect. Chim.*, **4**, 61 (1962); *Chem. Abstr.*, **59**, 12805 (1963).
(38) I. N. Lofgren, *Ark. Kemi, Mineral, Geol.*, **A22**, No. 18 (1946); *Chem. Abstr.*, **43**, 1021 (1949).
(39) A. A. Goldberg and W. Kelly, *J. Chem. Soc.*, 1919 (1948); *Chem., Abstr.*, **43**, 3014 (1949).
(40) D. E. Johnson, R. S. Bruenner, and A. J. Di Milo, *Ind. Eng. Chem., Prod. Res. Develop*, **5** (1), 53 (1966); *Chem. Abstr.*, **64**, 12485 (1966).
(41) G. Thompson and R. F. Lambert, U. S. Patent 3,268,544 (1966); *Chem. Abstr.*, **65**, 13715 (1966).
(42) R. F. Lambert, G. Thompson, and C. E. Kristofferson, *J. Org. Chem.*, **29**, 3116 (1964).
(43) P. E. Fanta and A. S. Deutsch, *ibid.*, **23**, 72 (1958).
(44) D. V. Kashelikar and P. E. Fanta, *J. Amer. Chem. Soc.*, **82**, 4927 (1960).
(45) K. Fukui, T. Kagiya, S. Narisawa, and T. Maeda, Japanese Patent 69 22,285 (1969); *Chem. Abstr.*, **71**, 124449 (1969).
(46) D. A. Tomalia, N. D. Ojha, and B. P. Thill, *J. Org. Chem.*, **34**, 1400 (1969).
(47) H. W. Heine and Z. Proctor, *ibid.*, **23**, 1554 (1958).

NaI in acetonitrile refluxed for 4 days gives a 47% yield of 2-ethoxy-2-oxazoline.[48,49]

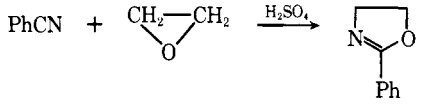
Furoylethylenimine isomerizes readily in the presence of iodide ion into 2-furyl-2-oxazoline, but isomerization of the 5-nitro analog goes with difficulty, owing to the reduced electron supply at the reaction site.[50]

1-(*p*-Nitrobenzoyl)-2,2-dimethylaziridine refluxed with NaI in acetone isomerizes to 2-(*p*-nitrophenyl)-4,4-dimethyl-2-oxazoline. The aziridine can be prepared by adding *p*-nitrobenzoyl chloride to a mixture of 2,2-dimethylaziridine, benzene, NaOH, and ice.[51-53]

Reactions of 9,10-epiminooctadecane with organic acids give mixtures of amides and oxazolines. With acetic acid, 2-methyl-4,5-di-*n*-octyl-2-oxazoline and 9-acetamido-10-hydroxyoctadecane are obtained.[54]

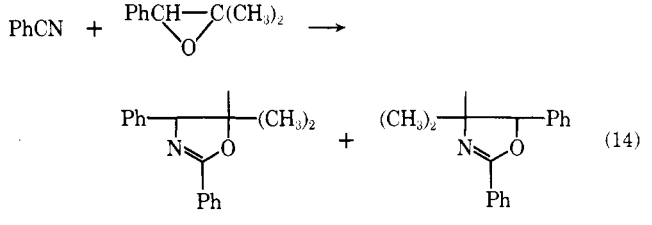
E. FROM EPOXIDES

The addition of aliphatic epoxides to nitriles in strong acid at low temperature gives 2-oxazolines upon neutralization with NaOH. Benzonitrile in concentrated H_2SO_4 at 0° treated with ethylene oxide and followed by neutralization with NaOH gives 2-phenyl-2-oxazoline. The reaction is general and can be used for the preparation of a variety of 2-oxazolines.[55]



(13)

Reaction of benzonitrile with *p*-chloro-2,2-dimethyl-1,2-styrene epoxide in dibutyl ether gives 4,4-dimethyl-2-phenyl-5-(*p*-chlorophenyl)-2-oxazoline. Reaction of 2,2-dimethylstyrene epoxide with benzonitrile in the same solvent gives 4,4-dimethyl-2,5-diphenyl-2-oxazoline and 5,5-dimethyl-2,4-diphenyl-2-oxazoline in 2:1 ratio as a result of two possible sites of the epoxy ring opening.[56] Since the reaction does not take place when dibutyl ether is omitted, the reaction must proceed through a carbonium ion stabilized by that solvent.

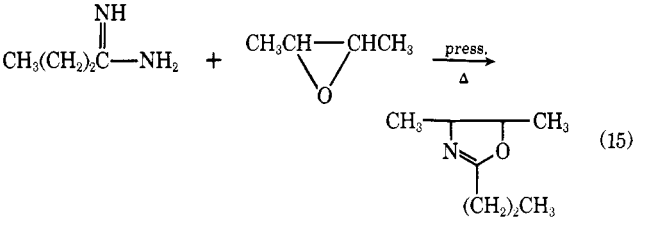


(14)

Benzoyl cyanide in chloroform and 1-methoxy-2,2-dimethyl-1-phenylethylene oxide with $SnCl_4$ forms a complex which after treatment with NaOH gives 5,5-dimethyl-4-methoxy-2,4-diphenyl-2-oxazoline.[57]

The action of epoxides on 2-substituted-2-thiazolines at 140–150° gives 2-substituted-5-substituted-2-oxazolines. From 2-phenyl-2-thiazoline and styrene epoxide the product is 2-phenyl-5-phenoxymethyl-2-oxazoline.[58,59]

The reaction of butyramidine with epoxides will form 2-propyl-2-oxazolines. Butyramidine and *cis*-2,3-butylene oxide heated 20 hr at 75° gives 42% *trans*-2-propyl-4,5-dimethyl-2-oxazoline. Butyramidine and *trans*-2,3-butylene oxide heated 5 hr at 100° under pressure yields 60% *cis*-2-propyl-4,5-dimethyl-2-oxazoline.[60,61]



(15)

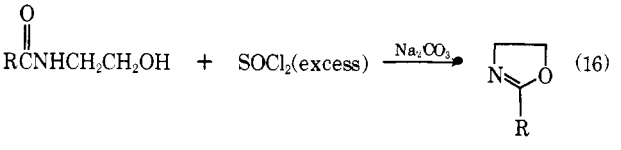
F. FROM GRIGNARD REAGENTS

The reaction of alkyl- and aralkylmagnesium halides on unsaturated azlactones (oxazolones) gives 4-substituted-5-keto-2-oxazolines with the alkyl or aralkyl group from the Grignard reagent adding to the unsaturated spot in the 4 position of the heterocyclic ring. For example, 2-phenyl-4-benzylidene-5-keto-2-oxazoline and anal kylmagnesium halide give 2-phenyl-4-(α-phenyl)alkyl-5-keto-2-oxazoline.[62]

From other work it has been reported that when *p*-methoxyphenylmagnesium bromide is used with an unsaturated azlactone, such as 2-phenyl-4-benzylidene-5-keto-2-oxazoline, the main product is 2,5,5-triphenyl-4-benzylidene-2-oxazoline.[63,64]

G. FROM REACTION OF $SOCl_2$ ON HYDROXYAMIDES

The reaction of $SOCl_2$ with 2-hydroxyalkylamides has been investigated thoroughly. In the cold with a large excess of $SOCl_2$, complex salts are formed. Refluxing with $SOCl_2$ gives about 85% yield to the 2-chloroalkylamide. Heating the chloro derivative in water gives about 80% yield to the amine hydrochloride ester. When the complex salt, formed from the large excess of $SOCl_2$, is decomposed in Na_2CO_3 solution, a yield of about 70% to the oxazoline is obtained.[65]



(16)

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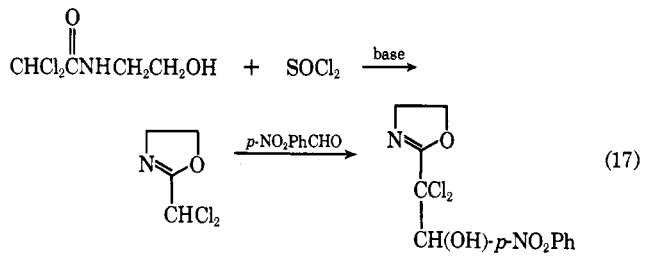
N-(2-Hydroxyethyl)-2,2-dichloroacetamide treated with $SOCl_2$ and made alkaline gives 2-dichloromethyl-2-oxazoline. The oxazoline can be condensed with *p*-nitrobenzaldehyde to give 2-[2-(*p*-nitrophenyl)-2-hydroxy-1,1-dichloroethyl]-2-oxazoline, a compound of possible medicinal interest.[66]



(17)

Although 2-benzamidomethyl-2-oxazoline hydrochloride is formed readily by the action of $SOCl_2$ on 2-hippuramidoethanol at 0°, the analogous reaction with hippuryl- and aceturylserine leads only to replacement of OH by Cl. The presence of a benzamido group in the 2 position causes the oxazoline to be a weaker base than when only methyl is in that position. This greatly increases the rate of decomposition in aqueous solution.[67]

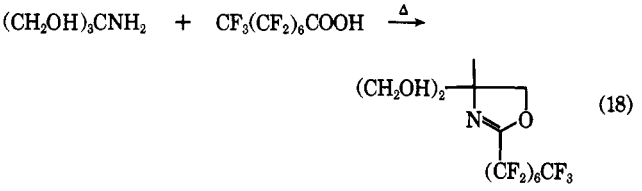
A boiling solution of *N*-(2-hydroxyethyl)-3-hydroxy-2-naphthamide in chloroform treated with $SOCl_2$ gives about 80% yield to 2-(2-hydroxy-3-naphthyl)-2-oxazoline hydrochloride.[68] D-*erythro*-1-(*p*-Nitrophenyl)-2-benzamido-1,3-propanediol in chloroform treated with $SOCl_2$ at low temperature gives L-*trans*-2-phenyl-4-hydroxymethyl-5-(*p*-nitrophenyl)-2-oxazoline.[69] The action of $SOCl_2$ on ethyl-2-benzamido-2-acetyl-3-hydroxypropionate in ether at 5° for 2 hr followed by treatment with aqueous Na_2CO_3 gives 2-phenyl-4-acetyl-4-carbethoxy-2-oxazoline. 2-Acetamido-2-acetyl-3-hydroxypropionohydroxamic acid and $SOCl_2$ treated in the same manner gives 2-methyl-4-acetyl-4-hydroxyaminocarbonyl-2-oxazoline.[70-72]

Polyamides treated with $SOCl_2$ give polyoxazoline hydrochlorides.[73]

H. HALOOXAZOLINES

Heating perfluoroalkylcarboxylic acids with an amino alcohol gives 2-perfluoroalkyl-2-oxazolines in good yields. For example, pentadecafluorooctanoic acid and 2-amino-2-hydroxymethyl-1,3-propanediol gives 2-pentadecafluoroheptyl-4,4-bis-(hydroxymethyl)-2-oxazoline.[74]

Perfluoroalkyl-2-oxazolines have been obtained in good yield by the action of ethylenimine in ether on a perfluoroacyl chloride in ether. Pentadecafluorooctoyl chloride and ethylenimine give the intermediate amide, which upon cyclization in NaOH solution yields 2-pentadecafluoroheptyl-2-oxazoline.[75]



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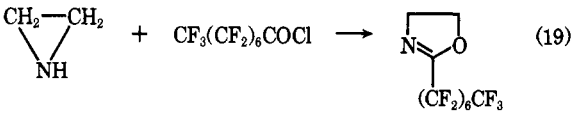
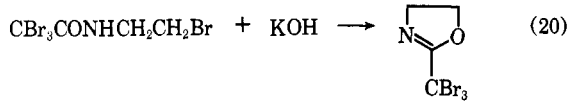


(19)

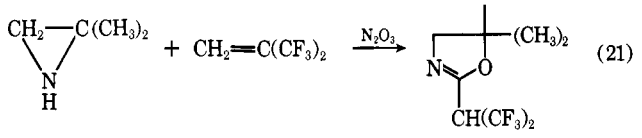
2-Perfluoroalkyl-2-oxazolines are also obtained from the reaction of 1-(perfluoroalkyl)aziridine and either KF, KBr, or KCl. 1-(Perfluorobutyryl)aziridine has been prepared by mixing ethylenimine in ether and triethylamine with perfluorobutyryl chloride at low temperature.[76]

2-(2-Perbromoalkyl)-2-oxazolines can be prepared by the reaction of an *N*-(2-haloalkyl)amide of a 2-perbromocarboxylic acid with KOH. For example, *N*-(2-bromoethyl)-2-tribromoacetamide added to a suspension of KOH in benzene at 20° yields 2-perbromomethyl-2-oxazoline.[77]



(20)

The reaction of 2,2-dimethylaziridine with 2,2-bis(trifluoromethyl)ketene in the presence of N_2O_3 gives 62% yield to 2-hexafluoroisopropyl-5,5-dimethyl-2-oxazoline.[78]



(21)

The reaction of *N*-[bis(trifluoromethyl)methylene]benzamide in heptane with cyclohexyl isocyanide gives 83% yield of 5-cyclohexylimino-4,4-bis(trifluoromethyl)-2-phenyl-2-oxazoline. Other related fluoroxazolines have been prepared in good yield by this general reaction.[79] For example, heating the benzamide with tris(ethoxy)methane for 15 hr at about 155° yields 2-phenyl-4,4-bis(trifluoromethyl)-5,5-diethoxy-2-oxazoline.[80]

2-Perfluoroalkyl-2-oxazolines have been prepared by cyclization of 2-chloroethyl perfluoroalkyl imidates.[81]

N-Benzoylphenylalanine with ketene yields 2-phenyl-4-benzyl-5-oxazolone, which upon treating with hexafluoroace-

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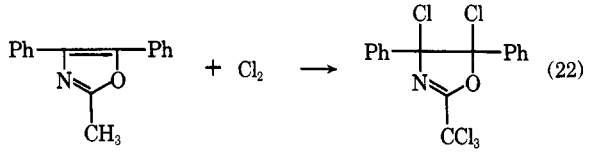
tone in pyridine gives 2-phenyl-4-benzyl-5,5-bis(trifluoromethyl)-2-oxazoline-4-carboxylic acid in 49% yield.[82]

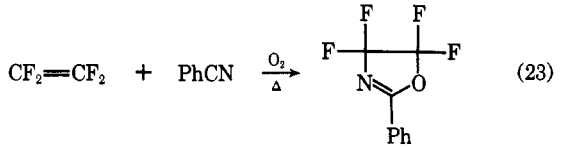
Refluxing *erythro*-3-phenyl-2,3-dibromopropyl iminobenzoate in toluene for only 5 min, and treating the filtrate with Na_2CO_3, gives *threo*-2-phenyl-4-(α-bromobenzyl)-2-oxazoline in about 50% yield.[83]

The reaction of 2-methyl-4,5-diphenoxazole with chlorine in chloroform after 14 days at room temperature yields 2-trichloromethyl-4,5-dichloro-4,5-diphenyl-2-oxazoline.[84]



(22)

Fluorinated 2-oxazolines have been prepared by the action of a fluoroolefin on an organic nitrile. For example, tetrafluoroethylene and benzonitrile heated under pressure at 175° while oxygen is injected gives 2-phenyl-4,4,5,5-tetrafluoro-2-oxazoline.[85]



(23)

Bromination in a carbon tetrachloride solution of *N*-(allyl)acetamide gives *N*-1-(2,3-dibromopropyl)acetamide and 2-methyl-5-bromomethyl-2-oxazoline.[86]

The addition of dry bromine in chloroform to 3-benzamidopropene in chloroform at low temperature gives about 45% yield to 2-phenyl-5-bromoethyl-2-oxazolinium bromide. Treatment with sodium acetate converts the quaternary compound to 2-phenyl-5-bromoethyl-2-oxazoline.[87]

Perfluoronitriles react with HCN in the presence of a basic catalyst to give α-iminoperfluoronitriles, which react with fluoro ketones to form fluorooxazolines.[88]

I. AMINOOXAZOLINES

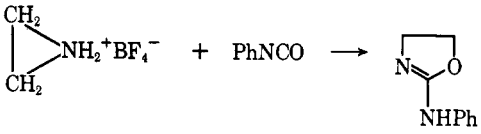
Aminooxazolines are of particular interest in therapeutic applications, and this interest has stimulated considerable research in the preparation of a variety of compounds.

Substituted 2-amino-2-oxazolines can be prepared by treating an amino alcohol with ethyl chloroformate and chlorinating with $SOCl_2$, which replaces the hydroxyl group with chlorine. Further treatment with PCl_5 gives 2-chloroalkyl isocyanate. Addition of a primary amine gives a substituted urea which cyclizes to yield a substituted 2-amino-2-oxazoline of the type where R can be α-naphthyl, 2,6-dimethylphenyl, phenyl, and tolyl.[89]

A method for making 2-diphenylamino-2-oxazoline from aziridine derivatives has been described. When *N*,*N*-diphenyl-1-aziridinecarboxamide is refluxed with acetone containing NaI, a good yield of 2-diphenylamino-2-oxazoline is obtained.[90,91]

(24)

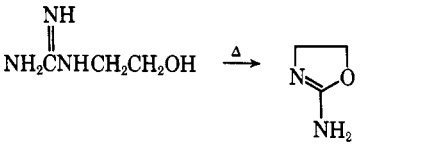
The reaction of aziridinium tetrafluoroborate with isocyanates gives good yields of 2-substituted aminooxazolines. Aziridinium tetrafluoroborate added to phenyl isocyanate gives about 90% yield of 2-phenylamino-2-oxazoline.[92]



(25)

When 2-bromo-1-ethylamine hydrochloride is mixed with cold KOH and treated with 1-naphthyl isocyanate, the crystallized product is *N*-(1-naphthyl)-*N'*-(2-bromoethyl)urea, which gives 2-(1-naphthylamino)-2-oxazoline when refluxed in water for a short time. Other naphthylaminooxazolines can be prepared from related starting materials.[93,94]

Cyclization takes place upon heating 1-(2-hydroxyethyl)-guanidine to form 2-amino-2-oxazoline in about 85% yield. 1-(2-Hydroxypropyl)guanidine, 1-(3-hydroxypropyl)guanidine, and the related -3-nitroguanidines undergo the same reaction to give similar products. The 1-(4-hydroxybutyl)-3-nitroguanidine does not cyclize.[95]



(26)

N,*N'*-Diphenylguanidinoethanols, prepared from diphenylcarbodiimide and amino alcohols, give 2-(substituted-amino)-2-oxazolines by thermal cyclization. Similar oxazolines can be prepared from *N*-substituted-*N'*-(2-hydroxyethyl)thioureas by the action of methyl iodide and sodium ethoxide.[96-98]

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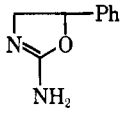
Substituted ureas, prepared from 2-chloroethyl isocyanate and *o*-toluidine (or *p*-toluidine, 2-chloro-6-methylaniline, or bornylamine), can be converted by refluxing with hot water to 2-arylamino-2-oxazolines.[99-102]

2-Bromoethyl isocyanate in ether added to 9-fluorenylamine in ether forms *N*-(9-fluorenyl)-*N'*-(2-bromoethyl)urea, which will convert to 2-(9-fluorenylamino)-2-oxazoline by boiling in water for a few minutes.[103]

2-(5,6,7,8-Tetrahydro-1-naphthylamino)-2-oxazoline is prepared by the action of 5,6,7,8-tetrahydronaphthylamine in chloroform with 2-bromoethyl isocyanate in chloroform and refluxing the intermediate substituted urea in water.[104] Also, 2-(*o*-toluidino)-2-oxazoline can be prepared from 2-chloroethyl isocyanate and 2-methylaniline.[105]

The reaction of a solution of α-(aminomethyl)benzyl alcohol hydrochloride and sodium acetate in methanol with BrCN in methanol and neutralization with K_2CO_3 give 2-amino-5-phenyl-2-oxazoline.[106,107]

$$PhCH(OH)CH_2NH_2{\cdot}HCl + NaOAc + BrCN \longrightarrow$$



(27)

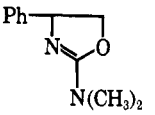
Propylene oxide and cyanamide in an aqueous medium at 50–60° for about 20 hr give a mixture of 2-[(2-hydroxypropyl)-amino]-5-methyl-2-oxazoline and 2-[bis(2-hydroxypropyl)-amino]-5-methyl-2-oxazoline.[108]

Styrene epoxide and cyanamide heated to 130–180° give a 42% yield of 2-(2-hydroxy-1-phenylethylamino)-4-phenyl-2-oxazoline, a 25% yield of 2-[bis(2-hydroxyl-1-phenylethyl)-amino]-4-phenyl-2-oxazoline, and a 26% yield of 2-[(1-phenyl-2-hydroxyethyl)(1,4-diphenyl-3-oxa-5-hydroxypentyl)amino]-4-phenyl-2-oxazoline.[109]

Heating 1-phenyl-1,2-dibromoethane with urea and treating with a mixture of aqueous HCl–benzene give 2-amino-4-phenyl-2-oxazoline. The 2-dimethylamino-4-phenyl-2-oxazoline can be prepared from refluxing 2-amino-2-phenyl-1-ethanol with dimethylaminoformyl chloride in benzene and heating the residue with $SOCl_2$.[110]

2-(2,4,6-Trimethylphenylamino)-2-oxazoline has been prepared from 2-amino-1-ethanol in aqueous NaOH with *N*-(dichloromethylene)-2,4,6-trimethylaniline in dioxane at about

$$PhCH(NH_2)CH_2OH + (CH_3)_2NCOCl \xrightarrow[\Delta]{SOCl_2}$$



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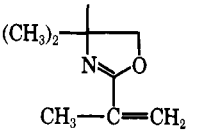
50°.[111,112] 2-(Cycloalkylamino)-2-oxazolines are prepared by treating cycloalkylimidocarbonyl chlorides with 2-amino-1-ethanol.[113]

Quaternization of 2-chloroxazoles and treatment with a primary amine give 2-aminooxazolines.[114] The reaction of 2-amino-1-nitraminoethane with ethanolic KOH gives 2-nitramino-2-oxazoline.[115]

J. VINYLOXAZOLINES

Vinyloxazolines have been prepared from the reaction of amino alcohols with acrylic esters. 2-Amino-2-methyl-1-propanol and methyl methacrylate refluxed briefly and then distilled in the presence of aluminum isopropoxide give 2-isopropenyl-4,4-dimethyl-2-oxazoline.[116-118]

$$(CH_3)_2C(NH_2)CH_2OH + CH_2{=}C(CH_3)COOCH_3 \longrightarrow$$



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Acryloyl halides and amino alcohols form acrylamides which cyclize when heated in the presence of an acid to give vinyloxazolines. 2-Amino-2-methyl-1-propanol and methacryloyl chloride give 2-isopropenyl-4,4-dimethyl-2-oxazoline in 60% yield.[119]

Vinyloxazolines have been prepared by the action of fatty acids on amino alcohols at about 230° to form an oxazoline which after reaction with formaldehyde can be dehydrated to the vinyl derivative. For example, 2-amino-2-hydroxymethyl-1,3-propanediol and linseed oil fatty acid give an oxazoline, which reacts with formaldehyde and, after dehydration at about 190°, gives the vinyloxazoline monomer. The vinyl group is located on the α-carbon of the alkyl group attached at the 2 position of the oxazoline ring.[120,121]

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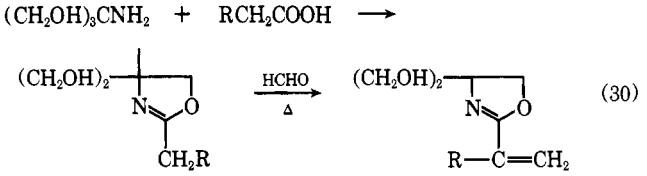


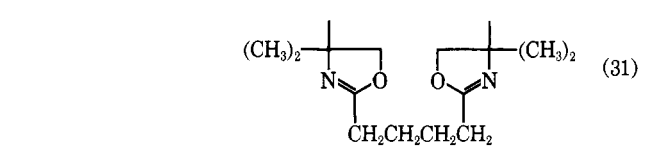
A similar procedure has been described where oxazolines are prepared from 2-amino-2-hydroxymethyl-1,3-propanediol and a dibasic acid. The vinyl derivative is obtained by condensation with formaldehyde followed by dehydration. It is claimed that ester formation occurs at the carboxyl group, linking three oxazoline groups to two alkyl groups from the dibasic acid.[122,123]

The reaction of β-(5-nitrofuryl)acryloyl chloride in benzene with ethylenimine gives a product which rearranges to 2-(5-nitrofuryl)vinyl-2-oxazoline when refluxed with *p*-toluidine in benzene.[124,125] Treating 1-(*p*-nitrobenzoyl)-2-vinylaziridine with I^- in acetone gives 2-(*p*-nitrophenyl)-5-vinyl-2-oxazoline.[125]

K. BIS(OXAZOLINES)

Bis(oxazolines) are formed from the reaction of dicarboxylic acids and amino alcohols. Adipic acid and 1-amino-2-propanol heated under a nitrogen blanket to about 200° give a 74% yield of distilled 2,2′-tetramethylenebis(5-methyl-2-oxazoline). A yield of 48% 2,2′-heptamethylenebis(5-methyl-2-oxazoline) has been obtained from the reaction of the same amino alcohol and azelaic acid.[126]

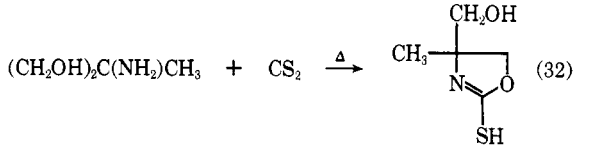
By a similar procedure bis(oxazolines) are prepared from 2-amino-2-methyl-1-propanol and dibasic acids. The reaction with adipic acid gave an 84% yield of distilled 2,2′-tetramethylenebis(4,4-dimethyl-2-oxazoline).[127]



L. MERCAPTOOXAZOLINES

The action of CS_2 on certain amino alcohols gives good yields of the mercaptooxazoline. For example, CS_2 with 2-amino-2-methyl-1,3-propanediol will give 2-mercapto-4-methyl-4-hydroxymethyl-2-oxazoline. A large excess of CS_2 is required and the reaction mixture is refluxed (ethanol) for several hours.[128]

The use of iodine catalyst with amino alcohols and CS_2 to give mercaptooxazolines has been reported. The reaction between 2-amino-2-methyl-1-propanol and CS_2 gave 2-



mercapto-4,4-dimethyl-2-oxazoline.[129] Also, the action of thiocarbonyl chloride on certain amino alcohols forms 2-mercaptooxazolines. For example, 3-amino-2-methyl-2-butanol and thiocarbonyl chloride give 2-mercapto-4,5,5-trimethyl-2-oxazoline.[130,131]

Aminoethylation of 2-thiooxazolidones will give products which rearrange in alkaline solution to 2-(mercaptoethylamino)-2-oxazolines.[132]

M. OXAZOLINES RELATED TO CHLORAMPHENICOL

Much use has been made of the chemistry of oxazolines and their relation to chloramphenicol for synthesis of that antibiotic. The oxazoline of prime interest is 2-dichloromethyl-4-hydroxymethyl-5-(*p*-nitrophenyl)-2-oxazoline. Synthesis of racemic and optically active forms of the compound has been by several related methods. Some of the widely used ones make use of the reaction between a β-phenylserine ester and ethyl 2,2-dichloroimidoacetate hydrochloride to form 2-dichloromethyl-4-carbethoxy-5-phenyl-2-oxazoline which can be converted to the 4-hydroxymethyl derivative by treatment with $LiAlH_4$.[133-149]

Other methods of interest include treating 2-dichloroacetamido-1-(*p*-nitrophenyl)-1,3-propanediol in pyridine with *p*-toluenesulfonyl chloride in benzene to obtain the oxazoline

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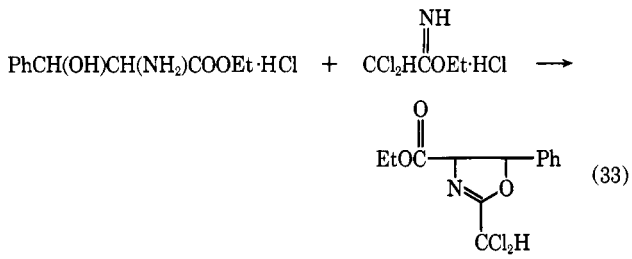

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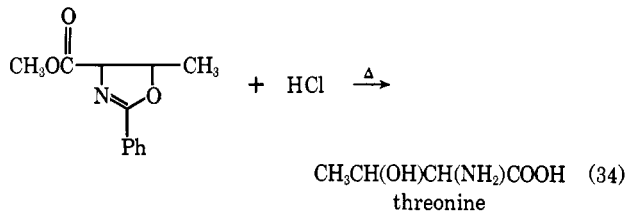
in good yields. The reaction of 1-(*p*-nitrophenyl)-2-amino-1,3-propanediol in pyridine with ethyl 2,2-dichloroimidoacetate hydrochloride gives the same compound.[150-153] Also, 2-dichloroacetamido-1-(*p*-nitrophenyl)-1,3-propanediol can be treated with acetyl chloride in the presence of pyridine to form the 3-acetoxy derivative, which gives the nitric ester with HNO_3 and upon treatment with NaOH gives the oxazoline.[154]

Cyclization of esters of 2-dichloroacetamido-1-(*p*-nitrophenyl)-1-chloro-3-propanol by treatment with NaOH solution gives the same oxazoline derivatives.[155-160] The 4-chloromethyl-substituted racemic and optically active forms have been prepared by treating 2-dichloroacetamido-1-(*p*-nitrophenyl)-,3-dichlorqpropane with dilute NaOH solution.[161,162]

N. OXAZOLINES RELATED TO THREONINE

Derivatives of allothreonine can be converted to threonine by treatment with a cyclizing and dehydrating agent to form the oxazoline derivative, and subsequent hydrolysis with acid or NaOH. The transformation is claimed to be due to inversion of the β-OH group during the oxazoline formation.

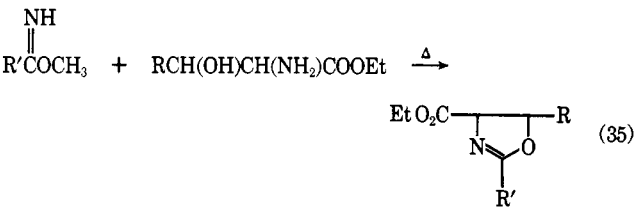
The methyl ester of *N*-benzoyl-DL-allothreonine with cold $SOCl_2$ forms 2-phenyl-5-methyl-4-carbomethoxy-2-oxazoline hydrochloride which gives DL-threonine when refluxed with 10% HCl.[163-170]



(34)
threonine

O. CARBALKOXY-SUBSTITUTED OXAZOLINES

Carbalkoxy-substituted 2-oxazolines have been prepared by several methods. One of the most popular involves the reaction of imino ethers with esters of α-amino acids. Reduction by various methods converts the carbalkoxy group to a hydroxymethyl group or hydroxycarbamoyl group.



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Refluxing ethyl *erythro*-2-amino-3-hydroxycaproate hydrochloride with methyl imidobenzoate and extracting after a short time with ether and water form the carbalkoxyoxazoline. *cis*-2-Phenyl-4-carbethoxy-5-propyl-2-oxazoline has been obtained from these reactants, while *trans*-2-phenyl-4-carbethoxy-5-propyl-2-oxazoline has been recovered from the reaction of ethyl *threo*-2-amino-3-hydroxycaproate.[171] Similar studies have been reported where carbalkoxyoxazolines are reduced with $LiAlH_4$ to give *cis*-2-phenyl-4-hydroxymethyl-5-alkyl-2-oxazoline.[172-174]

Methyl *threo*-2-amino-3-hydroxystearate treated with benzoyl chloride forms the benzamide derivative which gives *cis*-2-phenyl-4-carbomethoxy-5-pentadecyl-2-oxazoline when treated with $SOCl_2$.[175]

P. EFFECT OF STEREOCHEMISTRY

The effect of stereochemistry has been demonstrated in the reaction of *trans*- and *cis*-2-chlorocyclohexylamine. The *p*-nitrobenzamide of the transform could be converted to 2-(*p*-nitrophenyl)-4,5-tetramethylene-2-oxazoline, but the cis form would not cyclize, indicating that the trans form is better oriented for ring closure.[176,177]

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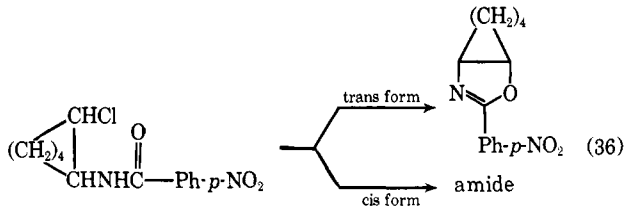

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Both *cis*- and *trans*-2-aminocyclohexanol form oxazolines when treated with ethyl imidobenzoate. The conversion of *cis*-2-aminocyclopentanol to oxazoline is easy, but *trans*-cyclopentanooxazoline cannot be prepared.[178] Stereochemical studies involving oxazolines indicate that *cis*-2-aminocyclotetradecanol can be changed to the transform by going through the *trans*-2-phenyl-4,5-dodecamethylene-2-oxazoline and hydrolyzing back to the amino alcohol using HCl. *trans*-2-Aminocyclopentadecanol can be obtained in 82% yield from *trans*-2-phenyl-4,5-tridecamethylene-2-oxazoline.[179]

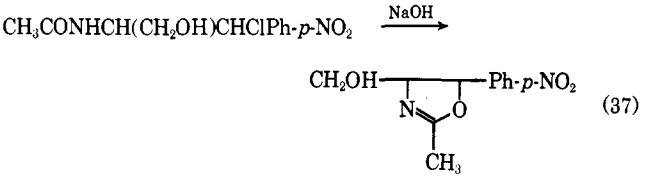
A stereospecific reaction was reported in the acid-catalyzed cyclization of *N*-thiobenzoyl derivatives of epimeric 1,2-amino alcohols. The threo epimers give exclusively *trans*-2-oxazolines, the erythro epimers give only 20–40% *cis*-2-oxazolines, and the main products are *trans*-2-thiazolines.[180]

1,2-*N*-Acylamino alcohols react with $SOCl_2$ according to the configuration to give either 2-oxazolines (with inversion) or a β-chloro amide (without inversion). For example, *erythro*-*N*-(1-methyl-2-phenyl-2-hydroxyethyl)-*p*-nitrobenzamide treated for a short time with $SOCl_2$ gives 2-(*p*-nitrophenyl)-4-methyl-5-phenyl-2-oxazoline, while on prolonged action of $SOCl_2$ a secondary reaction yields *erythro*-*N*-(1-methyl-2-phenyl-2-chloroethyl)-*p*-nitrobenzamide.[181]

Iodide ion catalyzes the isomerization of *cis*- and *trans*-1-*p*-nitrobenzoyl-2,3-dimethylaziridines and *trans*-1-*p*-nitrobenzoyl-2,3-diphenylaziridine into *cis*- and *trans*-2-*p*-nitrophenyl-4,5-dimethyl-2-oxazolines and *trans*-2-*p*-nitrophenyl-4,5-diphenyl-2-oxazoline, respectively.[53]

An oxazoline reaction has been illustrated as a means for changing *erythro*-1-phenyl-2-acetamido-1,3-propanediol into *threo*-1-phenyl-2-acetamido-1,3-propanediol. The erythro compound can be treated with $SOCl_2$ at low temperature and, after removal of excess $SOCl_2$ *in vacuo* and neutralization of the residue, *trans*-2-methyl-4-hydroxymethyl-5-phenyl-2-oxazoline is obtained. The oxazoline can be treated with a 20% solution of HCl, and the recovered product is *threo*-1-phenyl-2-acetamido-1,3-propanediol.[182]

DL-*threo*-3-(*p*-Nitrophenyl)-3-chloro-2-acetamido-1-propanol heated at 40° in ethanolic NaOH gives about 75% yield to DL-2-methyl-4-hydroxymethyl-5-(*p*-nitrophenyl)-*trans*-2-oxazoline. The fact that ring closure takes place through the carbon atom containing chlorine, rather than the one containing the OH group, indicates another route to preparing oxazolines containing a hydroxymethyl group on the oxazoline ring.[183]



(37)

The reaction of ethyl DL-threoninate hydrochloride with methyl benzimidate to give DL-*threo*-2-phenyl-5-methyl-4-carbethoxy-2-oxazoline has been used in studies involving determination of the D-threo configuration for elaiomycin.[184]

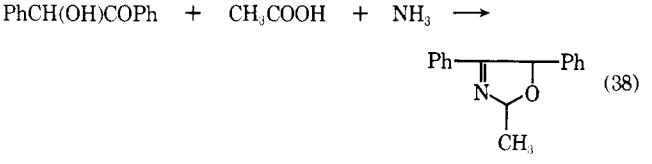
Q. 3-OXAZOLINES

3-Oxazolines can be obtained from the reaction of cyanamide with trifluoromethyl-substituted 4-oxazolidones, which are prepared from hexafluoroacetone, NaCN, and acetonitrile.

Also, the action of NaCN and diethyl sulfate on hexafluoroacetone gives a similar product, 2,2,5,5-tetrakis(trifluoromethyl)-4-ethoxy-3-oxazoline.[185,186]

4-Amino-3-oxazolines having halogenated hydrocarbon substituents in the 2 and 5 positions have been prepared by the action of hexafluoroacetone on powdered NaCN in acetonitrile with the addition of hexafluoroisopropylideneamine. A yield of 37% to 4-amino-2,2,5,5-tetrakis(trifluoromethyl)-3-oxazoline has been reported.[187]

A series of 3-oxazolines was synthesized using the general procedure of adding an α-hydroxy ketone to acetic acid and ammonia and extracting the product with ether. For example, the reaction of benzoin in ethanol with acetic acid and gaseous ammonia gave a 40% yield of distilled 2-methyl-4,5-diphenyl-3-oxazoline.[188]



(38)

Also, α-hydroxy-α-methyl ketones react with ammonia and aromatic aldehydes in the presence of $CaCl_2$ and NH_4Cl to give 2-aryl-3-oxazolines.[189,190]

The nitrile ylide, obtained from HCl cleavage of *N*-(α-chlorobenzylidene)-*p*-nitrobenzylamine upon treatment with benzaldehyde, gives about 37% yield of 2-(*p*-nitrophenyl)-4-phenyl-5-methyl-3-oxazoline.[191]

A compound identified as 2,4,5-trimethyl-3-oxazoline has been isolated from the volatile flavor compounds of boiled beef.[192]

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R. 4-OXAZOLINES

Very little work has been reported on the preparation of 4-oxazolines. However, claims are made for excellent yields when a substituted 4-oxazoline is prepared from naphthyl isocyanate and an α-methylaminoalkyl nitrile. For example, α-methylaminovaleronitrile in ether added to 1-naphthyl isocyanate in ether gives 100% 1-(1-cyanobutyl)-1-methyl-3-(1-naphthyl)urea, which can be converted quantitatively to 5-amino-3-methyl-2-(1-naphthylimino)-4-propyl-4-oxazoline when refluxed with sodium ethoxide in ethanol.[193]

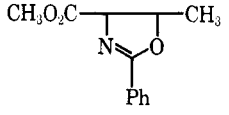
The thermal valence rearrangement of 4-isoxazolines to 2-acylaziridines and subsequently to 4-oxazolines has been reported.[194]

4-Oxazolines have been prepared by the addition of azomethine ylides to diphenylcyclopropenone.[195]

III. Reactions of Oxazolines

A. WITH ACIDS, ANHYDRIDES, METHYL ESTERS, AND BASE

Oxazolines hydrolyze with mineral acids. Advantage is taken of this property to make DL-threonine. 2-Phenyl-5-methyl-4-carbomethoxy-2-oxazoline hydrochloride and dilute HCl give a 70% yield of DL-threonine (α-amino-β-hydroxybutyric acid) (eq 39).[196] When alkaline hydrolysis is used the yield of DL-



$$\xrightarrow{HCl} CH_3CH(OH)CH(NH_2)COOH \quad (39)$$

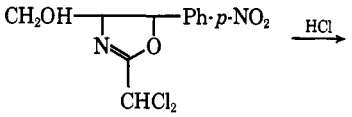
threonine

threonine is only 27%. If the oxazoline is hydrolyzed by boiling in water the product is *o*-benzoyl-DL-threonine methyl ester hydrochloride.[163,166,169]

Also, the ethyl ester of DL-*trans*-2-phenyl-5-methyl-2-oxazoline-4-carboxylic acid will hydrolyze in dilute NaOH solution to give DL-*o*-benzoylthreonine. Sodium ethoxide has been used to convert methyl *cis*-L-2-phenyl-5-methyl-2-oxazoline-4-carboxylate into *trans*-D-2-phenyl-5-methyl-2-oxamethyl-2-oxazoline-4-carboxylic acid.[197]

The D and L forms of *cis*-2-phenyl-4-carboxy-5-hydroxymethyl-2-oxazoline give α-amino-β,γ-dihydroxybutyric acid when treated with base and hydrolyzed with acid.[198]

Chloramphenicol can be prepared from an intermediate 2-oxazoline by treatment with dilute HCl at low temperature to open the ring. For example, 2-dichloromethyl-4-hydroxymethyl-5-(*p*-nitrophenyl)-2-oxazoline is converted with dilute HCl to 2-dichloroacetamido-1-(*p*-nitrophenyl)-1,3-propanediol (chloramphenicol)[199-202] (eq 40). However, if the oxazoline



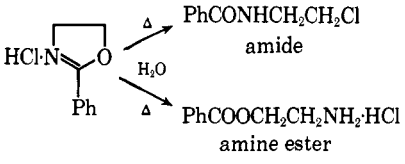
$$CHCl_2CONHCH(CH_2OH)CH(OH)Ph\text{-}p\text{-}NO_2 \quad (40)$$

in chloroform is heated at 40° for 5 min with HCl in ethanol, it is converted to 3-(*p*-nitrophenyl)-3-dichloroacetoxy-2-amino-1-propanol hydrochloride.[153]

Chloroamphenicol *O*-monosuccinate has been prepared in 84% yield by the action of succinic anhydride and sodium succinate on 2-dichloromethyl-4-hydroxymethyl-5-(*p*-nitrophenyl)-2-oxazoline at 110° for 45 min.[203,204]

Optically active forms of 2-amino-1-(*p*-nitrophenyl)-1,3-propanediol have been prepared by fission of 2-dichloromethyl-4-(*p*-nitrophenyl)hydroxymethyl-2-oxazoline with dry HCl. The threo form may be prepared by careful hydrolysis of *threo*-2-dichloromethyl-5-(*p*-nitrophenyl)-4-chloromethyl-2-oxazoline with dilute mineral acids.[152,205]

2-Phenyl-2-oxazoline hydrochloride will change on heating to give *N*-(2-chloroethyl)benzamide. The same compound heated in water for only 2 min gives the hydrochloride of 2-aminoethyl benzoate. Rearrangement of the hydrochloride of 2-(*p*-nitrophenyl)-5-(diethylaminomethyl)-2-oxazoline on a steam bath gives *N*-(3-diethylamino-2-chloropropyl)-*p*-nitrobenzamide hydrochloride.[63]



(41)

DL-4-Carbohydroxamido-2-phenyl-2-oxazoline in dry dioxane treated with HCl in dry dioxane and heated for a few minutes on a steam beath gives *N*-(1-carbohydroxamido-2-chloroethyl)benzamide. Treating the oxazoline with dilute NaOH gives the sodium salt of 4-carboxy-2-phenyl-2-oxazoline.[206]

4-Carbethoxy-5-(*p*-nitrophenyl)-2-phenyl-2-oxazoline is converted in dry dioxane to *erythro*-ethyl 2-benzamido-3-(*p*-nitrophenyl)-3-chloropropionate when heated on a steam bath in the presence of HCl in dioxane.[207,208]

The position at which alkyl- or aryl-substituted oxazoline rings open depends upon the reagent used. Heating 2-(*p*-nitrophenyl)-2-oxazoline with benzoyl chloride gives *N*-(2-chloroethyl)-*N*-benzoyl-*p*-nitrobenzamide. The same product is obtained when 2-phenyl-2-oxazoline is treated with *p*-nitrobenzoyl chloride. Heating 2-phenyl-2-oxazoline with *p*-nitrobenzoic acid for several minutes on a steam bath gives 2-benzamidoethyl *p*-nitrobenzoate. Heating 2-(*p*-nitrophenyl)-2-oxazoline with benzoic acid for 15 min at 130° yields-2-(*p*-nitrobenzamido)ethyl benzoate. Addition of thiobenzoic acid to 2-phenyl-2-oxazoline gives β-benzamidoethyl thiol-

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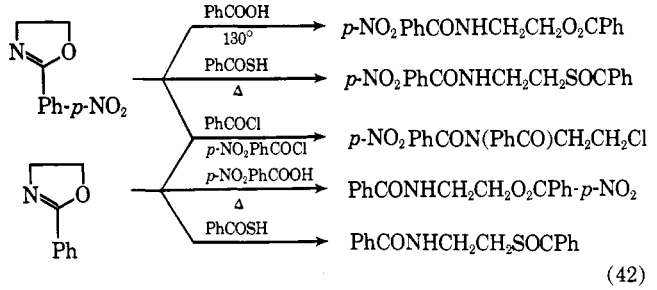
benzoate in an exothermic reaction. When equivalent amounts of 2-(*p*-nitrophenyl)-2-oxazoline and thiobenzoic acid are heated on a steam bath, the product is β-(*p*-nitrobenzamido)ethyl thiobenzoate.[60,209]

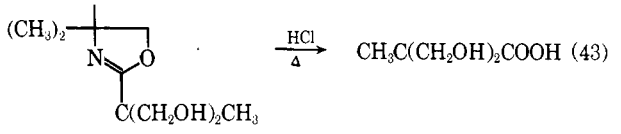


(42)

Reactions involving the effect of potassium acetate, acetic anhydride, and acetic acid on DL-*threo*-2-phenyl-4-(phenylhydroxymethyl)-2-oxazoline show that acetic acid is more effective in opening the oxazoline ring. The ring fails to open when treated with potassium acetate–acetic anhydride; instead the acyl derivative forms.[210]

The pH of partially neutralized solutions of 2-methyl-2-oxazoline changes with time, with an initial rise followed by a slower drop. The changes are due to conversion to *O*-acetylethanolamine and then to *N*-acetylethanolamine.[211–213]

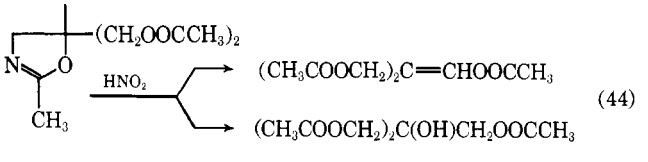
Acid hydrolysis of certain 2-substituted-2-oxazolines will convert to neo acids. For example, 2-[1,1-bis(hydroxymethyl)-ethyl]-4,4-dimethyl-2-oxazoline treated with concentrated HCl, diluted with water, and refluxed for 3 hr gives 2,2-bis-(hydroxymethyl)propionic acid.[214]



(43)

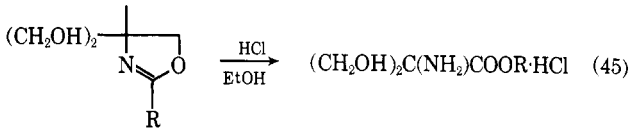
Nitration of the phenyl group of 2-methyl-5-phenyl-2-oxazoline sulfate, to give the *p*-nitrophenyl derivative, has been accomplished by treatment with HNO_3 at low temperature.[215]

The reaction of HNO_2 (from aqueous HCl and $NaNO_2$) with oxazoline diesters such as 2-methyl-5,5-bis(acetoxymethyl)-2-oxazoline gives triester derivatives, 2,2-bis(acetoxymethyl)-ethenyl acetate and 2,2-bis(acetoxymethyl)-2-hydroxyethyl acetate.[216]



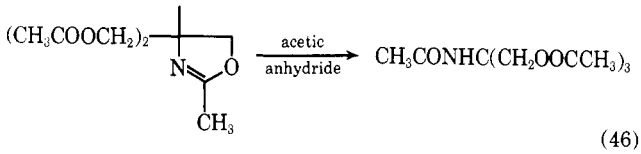
(44)

When a mixture of concentrated HCl and a 2-substituted-4,4-bis(hydroxymethyl)-2-oxazoline in absolute alcohol is allowed to stand for 30 min, cleavage occurs at the nitrogen to form 2-amino-3-hydroxy-2-(hydroxymethyl)propyl ester hydrochloride.[217]



(45)

Treatment of a variety of oxazolines with anhydrides of fatty acids, followed by addition of water, opens the oxazoline ring to give the corresponding ester amide. Refluxing 2-methyl-4,4-bis(acetoxymethyl)-2-oxazoline with acetic anhydride and then mixing with aqueous NaCl gives tris(acetoxymethyl)acetamidomethane in good yield.[218]



(46)

Oxazolines having a hydroxymethyl group in the 4 position and a long-chain alkyl group in the 2 position have been allowed to react with methyl acrylate in the presence of sodium methoxide at 50–70° for 2 hr to form methyl [(2-alkyl-4-methyl-4-oxazolinyl)methoxy] propionate. The sodium salt of that compound, having improved water solubility, has been obtained by reaction with aqueous NaOH.[219]

A solution of *trans*-2-phenyl-4,5-dodecamethylene-2-oxazoline in ethanol boiled for 18 hr with concentrated HCl gives good yields of *trans*-2-aminocyclotetradecanol.[179]

Heating certain aminooxazolines with dilute KOH in methanol for about 1 hr at reflux gives the amino alcohol. For example, from 2-(2-hydroxypropylamino)-5-methyl-2-oxazoline the amino alcohol formed in about 90% yield is 1-amino-2-propanol.[220]

Treating 2-oxazolines with aromatic hydrocarbons in the presence of Friedel–Crafts catalysts at elevated temperature will convert the oxazoline to diamines upon addition of an inorganic acid. 2-Methyl-2-oxazoline in benzene and $AlCl_3$ gives bis(2-aminoethyl)benzene in low yield.[221]

B. TO FORM POLYMERS

An oxazoline of the type where two or more oxazoline rings are joined at the 2 position by an aliphatic, aromatic, cycloaliphatic, or heterocyclic group will form polymers when heated with polycarboxylic acids. Condensation with a dibasic acid gives long-chain products which have alternate ester and amide groups.[222]

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Poly(2-isopropenyl-4,4-dimethyl-2-oxazoline) heated with methyl *p*-toluenesulfonate gives poly(2-isopropenyl-3,4,4-trimethyloxazolinium *p*-tosylate), which is hydrolyzed readily in dilute alkali to a copolymer of $CH_2{=}C(CH_3)CON(CH_3)C(CH_3)_2CH_2OH$ and $CH_2{=}C(CH_3)CO_2CH_2C(CH_3)_2NHCH_3$.[223]

Oxazolines of the type where two or more hydrogens are present on the oxazoline ring can be polymerized in the presence of cation-active catalysts. For example, 2-propyl-2-oxazoline in the presence of a small amount of *p*-nitrobenzenediazonium fluoroborate and heated to 120–130° for 15 hr gives a hard thermoplastic polymer.[224,225]

The reaction of bis(oxazolines) with dibasic acids gives poly(ester amides). The polymer from 2,2′-ethylenebis(2-oxazoline) and adipic acid has a melting range of about 145–155°.[226]

2-Substituted-2-oxazolines polymerize at about 70° in the presence of $SnCl_4$ catalyst, with ring opening between the 1–5 bond to give the *N*-acyl-substituted polyethylenimine structure.[227]

When a vinyloxazoline, such as 2-isopropenyl-2-oxazoline, is polymerized under the same conditions, the polymer contains an oxazoline ring in the chain. Anionic catalysts have no effect upon the polymerization.[228]

Purification for polymerization studies of 2-phenyl-2-oxazoline has been accomplished by mixing with a small amount of benzoyl chloride and distilling the oxazoline under reduced pressure. Pure oxazoline is recovered in high yield. The pure oxazoline polymerizes in the presence of an acid catalyst at about 140°. The technical-grade oxazoline will not polymerize at the same catalyst level, but when the catalyst content is increased about threefold, polymerization takes place.[229]

2-Substituted-2-oxazolines polymerize in the presence of $BF_3 \cdot Et_2O$ catalyst when heated to 60° for 4 hr in a sealed tube. The polymer contains recurring unit of $-N(COR)(CH_2CH_2)-$. Copolymers result from mixtures of different oxazolines, for example, from 2-methyl- and 2-heptyl-2-oxazoline. Other suitable catalysts include the perchlorate salt of the oxazoline.[230–232] 2-Substituted-2-oxazolines with substituents in the 4 or 5 positions essentially cannot be polymerized, apparently because of steric hindrance.

Polymerization of 2-pentyl-2-oxazoline in solvents containing various functional groups indicate that many solvents have no interaction or moderate interaction, whereas others interfere extensively, in some cases preventing polymerization.[233,234]

2-Alkyl- and 2-aryl-2-oxazolines have been polymerized in the presence of BF_3 to give poly(*N*-aroyl)aziridines and poly(*N*-acyl)aziridines ranging in molecular weight from 3500 to 7500 (35 to 50 oxazoline units per chain).[235]

2-Alkenyl-2-oxazolines can be homopolymerized, or copolymerized with other olefinically unsaturated compounds. For example, 2-isopropenyl-2-oxazoline gives a polymer when mixed with butyl acrylate and methyl methacrylate in the presence of azobisisobutyronitrile at 75° for 3 hr. A mixture of xylene and butanol is a satisfactory solvent for the polymerization. The homopolymer of poly(2-isopropenyl-2-oxazoline) can be prepared in a similar manner.[236]

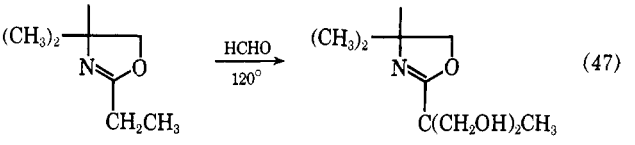
Triethylamine has been used in similar polymerizations involving these monomers to give linear rather than cross-linked polymers.[237] Copolymerization of CO with 2-phenyl-2-oxazoline gives a polymer which is probably poly(*N*-benzoyl-β-alanine).[238]

Hydroxyalkyl-substituted 2-oxazolines will react with polycarboxylic acids to give resins. For example, a mixture of 2-heptadecadienyl-4,4-bis(hydroxymethyl)-2-oxazoline, trimellitic anhydride, tetrahydrofurfuryl alcohol, and phthalic anhydride gives a polyester resin.[239]

Cross-linked homopolymers of 2-hydroxyalkyl-2-oxazolines have been prepared in the presence of cationic catalysts at 80–250°. Specifically, 2-(hydroxymethyl)-2-oxazoline and a small amount of catalyst [2-(*p*-chlorophenyl)-2-oxazoline perchlorate] in a sealed polymerization tube under reduced pressure heated for 2 hr at 100° and 2.5 hr at 160° give an insoluble, cross-linked polymer.[14]

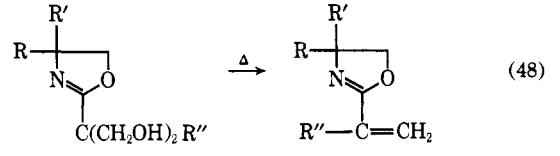
C. WITH ALDEHYDES

The reaction of paraformaldehyde with 2-alkyl-2-oxazoline at about 120° gives the 2-[1,1-bis(hydroxymethyl)alkyl]-2-oxazoline condensation product. From 2-ethyl-4,4-dimethyl-2-oxazoline and paraformaldehyde at 120° the product is 2-[1,1-bis(hydroxymethyl)ethyl]-4,4-dimethyl-2-oxazoline.[214]



(47)

Vinyloxazolines are prepared by the action of paraformaldehyde on 2-alkyl-4,4-substituted-2-oxazolines. The reaction first forms the condensation product, and then at high temperature dehydration occurs to give the vinyl derivative. The products obtained are 2-alkylethenyl-4,4-substituted-2-oxazolines.[120]



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(232) W. Seeliger and W. Thier, German Patent 1,263,300 (1968); *Chem. Abstr.*, **68**, 96350 (1968).

(233) A. Levy and M. Litt, *J. Polym. Sci., Part A-1*, **6**, 57 (1968); *Chem. Abstr.*, **68**, 69417, 69418 (1968).

(234) A. J. Levy and M. H. Litt, U. S. Patent 3,458,456 (1969); *Chem. Abstr.*, **71**, 71180 (1969).

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(236) F. Riemhofer, W. Seeliger, and F. Stuerzenhofecker, German Patent 1,261,261 (1968); *Chem. Abstr.*, **68**, 70273 (1968).

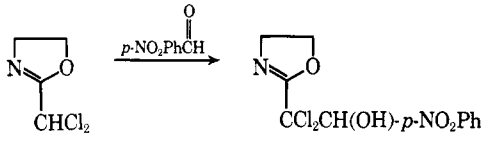
(237) Chemische Werke Huels A.-G., French Patent 1,547,176 (1968); *Chem. Abstr.*, **71**, 40373 (1969).

(238) T. Kagiya, S. Narisawa, T. Ichida, N. Ota, and K. Fujui, *Kogyo Kagaku Zasshi*, **69**, 2220 (1966); *Chem. Abstr.*, **67**, 11911 (1967).

(239) T. J. Miranda and H. R. Herman, U. S. Patent 3,438,943 (1969); *Chem. Abstr.*, **70**, 116324 (1969).

Benzaldehyde and other aromatic aldehydes react with 2-alkyl-2-oxazolines to form phenylethenyloxazolines. The reaction of benzaldehyde with 2-methyl-4,4-dimethyl-2-oxazoline gives 2-phenylethenyl-4,4-dimethyl-2-oxazoline. Hydrolysis of the latter gives cinnamic acid in high yield.[240]

The reaction of 2-dichloromethyl-2-oxazoline with *p*-nitrobenzaldehyde occurs under mild conditions to give 2-[(*p*-nitrophenyl)-2-hydroxy-1,1-dichloroethyl]-2-oxazoline.[66]

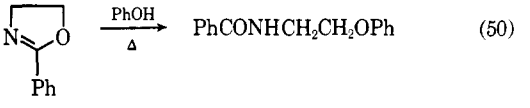


(49)

D. WITH PHENOLS

Substituted 2-oxazolines react with phenol or thiophenol in the absence of water to give ethers, thioethers, and carboxamides.

A mixture of 2-phenyl-2-oxazoline and phenol refluxed for 7 hr forms *N*-[1-(2-phenoxyethyl)]benzamide (eq 50). 2-



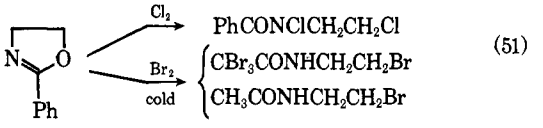
(50)

Phenyl-2-oxazoline and hydroquinone give 1,4-bis(2-benzamidoethoxy)benzene. The reaction of thiophenol with 2-2-phenyl-2-oxazoline yields the thioether *N*-(2-phenylthioethyl)benzamide.[241]

E. WITH HALOGENS, PHOSGENE, AND ALKYL HALIDES

The reaction of 2-phenyl-2-oxazoline with chlorine goes smoothly with ring opening to form the *N*-chloramide, *N*-(2-chloroethyl)-*N*-chlorobenzamide. The action of bromine on the oxazoline yields *N*-bromo-2-phenylazolinium bromide. The addition of bromine to 2-alkyl-2-oxazolines in the cold gives a mitxure of *N*-(2-bromoethyl)tribromoacetamide and *N*-(2-bromoethyl)acetamide. There is no partial bromination at the α-carbon. The addition of chlorine to 2-alkyl-2-oxazolines gives partially chlorinated products. 2-(1-Monochloroalkyl)-2-oxazolines can be obtained by using an excess of the oxazoline. With 2-ethyl-2-oxazoline and equal molar amounts of chlorine, mixtures of *N*-(2-chloroethyl)propionamide, *N*-(2-chloroethyl)-2-chloropropionamide, and *N*-(2-chloroethyl)-2,2-dichloropropionamide are obtained. The chlorinated amide can be converted to 2-trichloroalkyl-2-oxazolines by treatment with alkali and further chlorination.[19,242,243]

Oxazolines having hydroxymethyl substitution on the ring react with phosgene to form the chloroformoxymethyl derivative. For example, 2-aryl-4-hydroxymethyl-4-methyl-2-oxazoline in chloroform treated with a toluene solution of phosgene gives the 2-aryl-4-(chloroformoxymethyl)-4-methyl-2-



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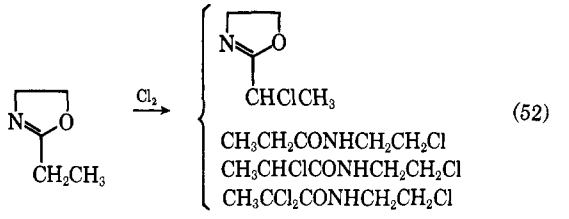
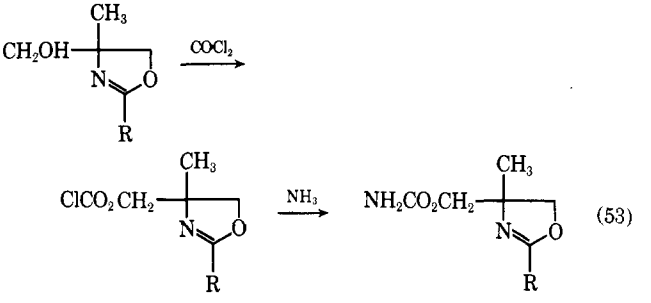


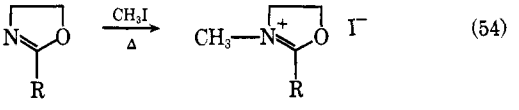
(52)

oxazoline. This compound can be converted to the corresponding 4-carbamoyl derivative by treatment with NH_3.[244,245]



(53)

Oxazolines react with alkyl halides to give the corresponding quaternary compound. For example, the oxazolinium salt of 2-cyclohexyl-4,4-dimethyl-2-oxazoline can be prepared by treating the oxazoline with methyl iodide in nitromethane at 70° (eq 54). Oxazolinium iodides in methanol, treated with



(54)

$NaBH_4$ at below 5°, are reduced to the corresponding oxazolidine. 2-(2-Phenylethyl)-3,4,4-trimethyl-2-oxazolinium iodide gives 2-(2-phenylethyl)-3,4,4-trimethyloxazolidine.[246,247]

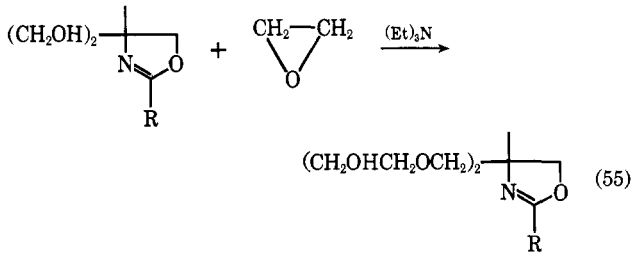
N-Methyl-2,4,4-substituted-2-oxazolinium iodides will hydrolyze rapidly at a high pH, while at low pH hydrolysis is slow. The products are the corresponding amine esters. The methiodide salt of 2-methyl-4,4-dimethyl-2-oxazoline gives 2-methylamino-2-methylpropyl formate.[248,249]

Oxazolinium salts have been used in the preparation of 1-halo-3-amino-2-alkanones. For example, 2,4-dimethyl-4-isopropyl-5-bromomethylene-2-oxazolinium bromide in ethanol at room temperature gives 1-bromo-3,4-dimethyl-3-amino-2-pentanone hydrobromide.[250,251]

(240) H. L. Wehrmeister, *J. Org. Chem.*, **27**, 4418 (1962).
(241) A. Jager, German Patent 1,062,253 (1959); *Chem. Abstr.*, **55** 13380 (1961).
(242) E. Aufderhaar and W. Seeliger, *Justus Liebigs Ann. Chem.*, **701**, 166 (1967); *Chem. Abstr.*, **66**, 94933 (1967).
(243) K. D. Hesse and W. Seeliger, *Justus Liebigs Ann. Chem.*, **724**, 166 (1969); *Chem. Abstr.*, **71**, 61269 (1969).
(244) V. Rosnati and D. Misiti, *Rend. Ist. Super. Sanita*, **23**, 603 (1960); *Chem. Abstr.*, **55**, 5464 (1961).
(245) V. Rosnati and D. Misiti, *Gazz. Chim. Ital.*, **90**, 573 (1960); *Chem. Abstr.*, **55**, 15460 (1961).
(246) I. C. Nordin, *J. Heterocycl. Chem.*, **3**, 531 (1966); *Chem. Abstr.*, **66**, 46352 (1967).
(247) T. Taguchi and M. Kojima, *Pharm. Bull. (Tokyo)* **1**, 325 (1953); *Chem. Abstr.*, **49**, 10929 (1955).
(248) P. Allen, Jr., and J. Ginos, *J. Org. Chem.*, **28**, 2759 (1963).
(249) L. Oliveros and H. Wahl, *Bull. Soc. Chim. Fr.*, 2815 (1969); *Chem. Abstr.*, **71**, 129266 (1969).
(250) N. R. Easton, U. S. Patent 3,278,544 (1966); *Chem. Abstr.*, **66**, 46102 (1967).
(251) Eli Lilly and Co., French Patent 1,545,928 (1968); *Chem. Abstr.*, **71**, 123581 (1969).

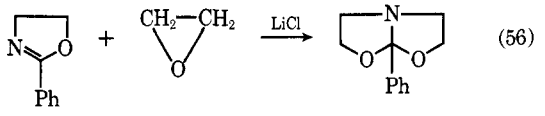
F. WITH EPOXIDES

Epoxides undergo base-catalyzed addition to hydroxymethyl-substituted 2-oxazolines to form hydroxyethyl ethers or polyethers depending on the ratio of epoxide to oxazoline. Ethylene oxide adds to 2-alkyl-4,4-bis(hydroxymethyl)-2-oxazoline in the presence of triethylamine to give 2-alkyl-4,4-bis(2-hydroxyethoxymethyl)-2-oxazoline.[252]



(55)

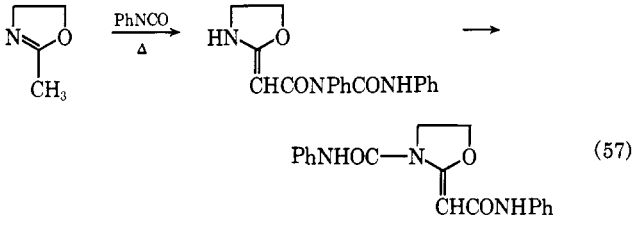
The reaction of an epoxide with 2-oxazolines having no active groups in the 4 and 5 positions and in the presence of LiCl catalyst forms 1-aza-4,6-dioxabicyclo[3.3.0]octane. From ethylene oxide and 2-phenyl-2-oxazoline the product is 1-aza-5-phenyl-4,6-dioxabicyclo[3.3.0]octane.[253]



(56)

G. WITH ISOCYANATES

Phenyl isocyanate reacts with 2-alkyl-2-oxazolines when hydrogens are present on the α-carbon of the 2-substituted group to give either mono- or disubstituted addition products. For example, 2-methyl-2-oxazoline and phenyl isocyanate, in a molar ratio of 1:2 and heated under anhydrous conditions for 2 hr at 80°, give about 80% disubstituted product. One group is attached at the ring nitrogen and one at the 2-methyl group of the oxazoline ring. The product is a disubstituted oxazolidine.[254]

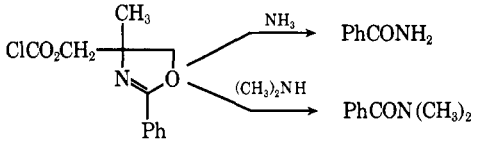


(57)

H. WITH AMINES

Certain amines react with oxazolines in various ways. The methyl ester of 2-(*o*-carboxyphenyl)-2-oxazoline is obtained from the reaction of the carboxyl group with cyanamide in ether. However, when 2-(*o*-carboxyphenyl)-2-oxazoline is allowed to react with aniline in ethanol, the product is 2-phenylamino-2-(*o*-carboxyphenyl)oxazolidine.[37]

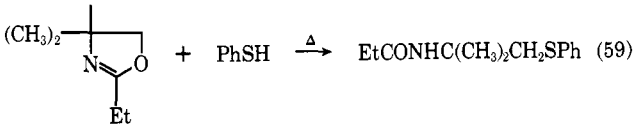
Treatment of 2-aryl-substituted 2-oxazolines with ammonia or methylamine opens the oxazoline ring and forms a benzamide. For example, when substituted oxazolines such as 2-aryl-4-chlorocarboxymethyl-4-methyl-2-oxazolines are treated with ammonia or dimethylamine at about 80° in a sealed tube with dry dioxane, the main product of the reaction is benzamide or *N*,*N*-dimethylbenzamide.[255]



(58)

I. WITH AROMATIC THIOLS AND SULFIDES

Reaction of aromatic thiols with oxazolines causes ring opening and amide formation, with addition of the thiol to the original oxazoline ring. A mixture of 2-ethyl-4,4-dimethyl-2-oxazoline and thiophenol refluxed for 6 hr gives 98% *N*-(2-phenylthio-1,1-dimethylethyl)propionamide.[256]



(59)

The reaction of a thiol with an oxazoline in an organic solvent at 0–100° gives an intermediate which upon hydrolysis with HCl gives 2-aminoalkanethiols. Thiobenzoic acid in pyridine and 2-methyl-4,4-bis(hydroxymethyl)-2-oxazoline yields a mixture which, with HCl hydrolysis, gives about a 70% yield of 2-amino-2-mercapto-1,3-propanediol.[257]

Reaction of a sulfide with 2-oxazolines opens the ring and forms the thioamide derivative. For example, the reaction of $(NH_4)_2S$ with 2-phenyl-2-oxazoline at 30° gives *N*-(2-hydroxyethyl)thiobenzamide.[258]

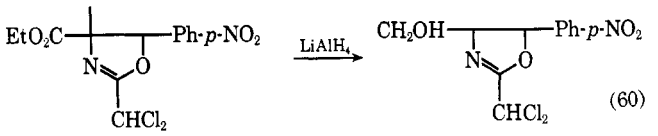
J. OXIDATION

Oxidation of bis(hydroxymethyl)-substituted 2-oxazolines with $KMnO_4$ provides a means for obtaining β-hydroxy-α-amino acids. For example, 2-phenyl-4,4-bis(hydroxymethyl)-2-oxazoline (prepared from benzoic acid and 2-amino-2-hydroxymethyl-1,3-propanediol) treated with $KMnO_4$ gives 2-amino-2-hydroxymethylmalonic acid.[3]

K. REDUCTION

Reduction of a carbalkoxy group on the oxazoline ring using $LiAlH_4$ gives the hydroxymethyl group. For example, 2-dichloromethyl-4-carbethoxy-5-(*p*-nitrophenyl)-2-oxazoline has been reduced by this procedure to give 2-dichloromethyl-4-hydroxymethyl-5-(*p*-nitrophenyl)-2-oxazoline. Wide use has been made of this property in the preparation of chloramphenicol, which can be obtained by hydrolysis of the hydroxymethyloxazoline[136,139,144,172,174,259–261] (eq 60). Reduction

(252) G. N. Butter and J. A. Frump, Belgian Patent 618,474 (1962); *Chem. Abstr.*, **58**, 11367 (1963).
(253) R. Feinauer and W. Seeliger, *Justus Liebigs Ann. Chem.*, **698**, 174 (1966); *Chem. Abstr.*, **66**, 37857 (1967).
(254) R. Nehring and W. Seeliger, *Justus Liebigs Ann. Chem.*, **698**, 167 (1966); *Chem. Abstr.*, **66**, 37807 (1967).
(255) V. Rosnati and D. Misiti, *Tetrahedron*, **9**, 175 (1960); *Chem. Abstr.*, **54**, 21047 (1960).
(256) H. L. Wehrmeister, *J. Org. Chem.*, **28**, 2587 (1963).
(257) C. R. Bresson, U. S. Patent 3,351,664 (1967); *Chem. Abstr.*, **68**, 95331 (1968).
(258) A. A. Goldberg and W. Kelly, *J. Chem. Soc.*, 1919 (1948).
(259) I. Felkin, H. Felkin, and Z. Welvart, *C. R. Acad. Sci.*, **234**, 1789 (1952); *Chem. Abstr.*, **47**, 2139 (1953).
(260) F. Hoffmann-LaRoche & Co., A.-G., Swiss Patent 275,968 (1951); *Chem. Abstr.*, **47**, 1739 (1953).
(261) M. Viscontini, G. Odasso, and W. Freitag, *Helv. Chim. Acta*, **49**, 1720 (1966); *Chem. Abstr.*, **65**, 13815 (1966).


(60)

of an ester group on an oxazoline to the hydroxymethyl group has been accomplished also with $NaBH_4$ or KBH_4 in various solvents.[262]

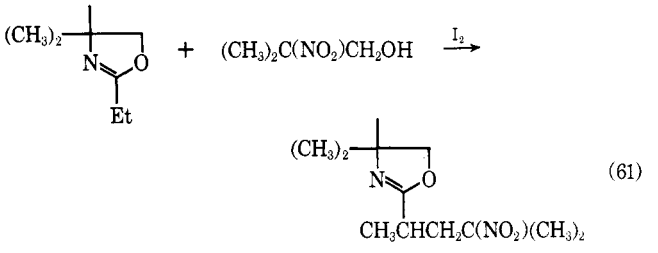
The action of hydroxylamine on oxazolines containing a carbalkoxy group on the oxazoline ring will convert that group to a hydroxycarbamoyl group. For example, 2-phenyl-4-carbethoxy-2-oxazoline with hydroxylammonium chloride (in hot anhydrous ethanol and Na) is converted in 88% yield to 2-phenyl-4-hydroxycarbamoyl-2-oxazoline.[263-265]

L. PYROLYSIS

2-Alkyl- (and aryl-) 4-methyl- (and -4,4-dimethyl-) 2-oxazolines can be pyrolyzed at 500–600° to give products of the general structure $RCONHCH_2CR'{=}CH_2$, where R is alkyl or aryl and R′ is H or methyl. For example, heating 2-ethyl-4,4-dimethyl-2-oxazoline at 500° gives *N*-methallylpropionamide, which can be converted in concentrated H_2SO_4 at 30° to 2-ethyl-5,5-dimethyl-2-oxazoline.[266,267] Thermal rearrangement of 2-(*o*-carboxyphenyl)-2-oxazoline gives *N*-(2-hydroxyethyl)-phthalimide.[30]

M. WITH NITRO ALCOHOLS

Nitro alcohols react with 2-substituted-2-oxazolines which have an active hydrogen on the α-carbon of the group attached at the 2 position. The action of 2-nitro-2-methyl-1-propanol on 2-ethyl-4,4-dimethyl-2-oxazoline in the presence of iodine gives 2-[1-(1,3-dimethyl-3-nitrobutyl)]-4,4-dimethyl-2-oxazoline.[268]


(61)

N. WITH PHOSPHORYLATING AGENTS

The action of diisopropyl phosphofluoridate in aqueous $NaHCO_3$ at 37° on 2-methyl-2-oxazoline, 2-phenyl-2-oxazoline, and 2-phenyl-4-carbamoyl-2-oxazoline has been investigated. The 2-methyl reacts faster than the 2-phenyl-2-oxazoline, and the 4-substituted oxazoline does not react. The reaction product, after acid hydrolysis, is *O*-phosphoryletha-nolamine.[269] The reaction of diisopropyl phosphochloridate with 2-methyl-2-oxazoline at room temperature for 24 hr in $NaHCO_3$ buffer gives diisopropyl 2-acetoxyethylphosphoramidate in about 50% yield.[270,271]

IV. Applications

A. PROTECTIVE COATINGS

Oxazolines are used in large volume in the field of surface coatings. They are used in aqueous systems as emulsifiers or surface active agents. An effective dispersing agent for metallic aluminum pigment in water-base paints is 2-heptadecenyl-4,4-bis(hydroxymethyl)-2-oxazoline.[272]

Vinyloxazoline esters, prepared from amino alcohols, long-chain unsaturated fatty acids, and formaldehyde, are good drying oils for surface coatings.[120,273,274]

A polyester of soybean vinyloxazoline has been used in nitrocellulose-based coating compositions. The film applied on steel sheets has improved flexibility, better resistance to film failure by chalking or cracking, and a glossier appearance than a similar film from an oxidized alkyd resin.[121]

Oxazolines, oxazoline esters, and their vinyl derivatives, prepared from long-chain saturated or unsaturated fatty acids and amino alcohols, are useful plasticizers for ethyl cellulose compositions. Films from the plasticized ethyl cellulose are tough, flexible, strong, and clear.[275]

Terpolymers containing an oxazoline are useful in coating compositions. For example, styrene, 2-ethylhexyl acrylate, acetic acid, and catalyst in a suitable solvent and then 2-amino-2-hydroxymethyl-1,3-propanediol added give a mixture which can be converted to the oxazolino acrylate structure by heating. The polymer product blended with melamine–formaldehyde resin in aromatic solvent and applied on metal and baked gives a film which is clear, tough, and resistant to alkalies, solvents, and grease.[276,277]

Oxazoline resins suitable for use in surface coatings are prepared from 2-amino-2-hydroxymethyl-1,3-propanediol, linseed fatty acid, and itaconic acid. They are made water soluble by addition of 2-propanol and neutralization with an amine.[278,279]

Polymers useful as heat-hardening coatings have been prepared from a mixture of acrylates and vinyloxazolines. For example, butyl acrylate, methyl acrylate, and 2-isopropenyl-2-oxazoline polymerized in a mixture of xylene and butanol containing azobisisobutyronitrile give a product which has good adhesion to glass and excellent solvent resistance.[236,237]

(262) Farbenfabriken Bayer A.-G., British Patent 823,318 (1959); *Chem. Abstr.*, **54**, 5575 (1960).
(263) F. W. Holly and C. H. Stammer, U. S. Patent 2,772,281 (1956); *Chem. Abstr.*, **51**, 8145 (1957).
(264) F. W. Holly and C. H. Stammer, U. S. Patent 2,840,565 (1958); *Chem. Abstr.*, **53**, 4302 (1959).
(265) N. K. Kochetkov, N. F. Kucherova, M. Y. Karpeiskii, and V. M. Solov'ev, *Dokl. Akad. Nauk SSSR*, **109**, 950 (1956); *Chem. Abstr.*, **51**, 5047 (1957).
(266) H. L. Wehrmeister, *J. Org. Chem.*, **30**, 664 (1965).
(267) H. L. Wehrmeister, U. S. Patent 3,365,494 (1968); *Chem. Abstr.*, **68**, 77787 (1968).
(268) H. L. Wehrmeister, U. S. Patent 3,354,171 (1967); *Chem. Abstr.*, **68**, 39613 (1968).
(269) G. R. Porter, H. N. Rydon, and J. A. Schofield, *Nature*, **182**, 927 (1958); *Chem. Abstr.*, **53**, 6309 (1959).
(270) R. Greenhalgh, *Nature*, **189**, 829 (1961); *Chem. Abstr.*, **55**, 22287 (1961).
(271) R. Greenhalgh, *Can. J. Chem.*, **40**, 976 (1962); *Chem. Abstr.*, **57**, 10999 (1962).
(272) S. Evans, British Patent 873,232 (1958); *Chem. Abstr.*, **56**, 566 (1962).
(273) R. F. Purcell, Belgian Patent 624,495 (1963); *Chem. Abstr.*, **59**, 1846 (1963).
(274) R. F. Purcell, French Patent 1,367,518 (1964); *Chem. Abstr.*, **62**, 5447 (1965).
(275) L. E. Cockerham and R. F. Purcell, U. S. Patent 3,348,958 (1967); *Chem. Abstr.*, **68**, 14166 (1968).
(276) T. J. Miranda and H. R. Herman, U. S. Patent 3,208,981 (1965); *Chem. Abstr.*, **63**, 16616 (1965).
(277) T. J. Miranda, *J. Paint Technol.*, **39** (504), 40 (1967); *Chem. Abstr.*, **66**, 47370 (1967).
(278) W. J. DeJarlais, L. E. Gast, and J. C. Cowan, *J. Amer. Oil Chem. Soc.*, **43**, 41 (1966); *Chem. Abstr.*, **64**, 9950 (1966).
(279) W. J. DeJarlais, L. E. Gast, and J. C. Cowan, *J. Amer. Oil Chem. Soc.*, **44**, 126 (1967); *Chem. Abstr.*, **66**, 105964 (1969).

A high-molecular-weight linear polymer of 2-alkyl- or 2-aryl-2-oxazolines has been prepared by heating the oxazoline monomer in the presence of an oxazoline perchlorate catalyst. The polymer has improved solubility in alcohols, ketones, and esters, and the films have improved impact and flexural strength.[232]

Resins having varying degrees of hardness and flexibility, and which are useful as molding and coating compositions, have been obtained by the reaction of dimerized linoleic acid, 2-amino-2-hydroxymethyl-1,3-propanediol, and formaldehyde, followed by various amounts of maleic anhydride.[123]

Oxazoline wax, which is obtained by the reaction of an amino alcohol and a long-chain saturated fatty acid, in a toluene solution applied to enameled wire improves the coefficient of friction for electical coils.[280]

Thermosetting polyester resins containing an oxazoline are useful as insulating coatings for electrical conductors.[281-283]

Reaction products of bis(oxazolines) and Diels–Alder adducts give viscous oils of excellent drying qualities in a varnish.[284]

Polymeric imido esters prepared from maleic adducts of fatty acid esters and bis(oxazolines) are useful as modifiers for surface coatings and for molding compositions.[285]

Reaction products of succinic, phthalic, or naphthalic anhydride and a bis(oxazoline) are useful as additives for lubricating oils, and as modifiers for plastics.[286] Also, the reaction products of an ester gum, maleic anhydride, and 2-alkenyl-2-oxazolines can be used as lube-oil additives, plasticizers, modifiers, or film-forming materials.[287]

Polymeric imido esters from maleic heteropolymers and 2-alkyl- or 2-alkenyl-2-oxazolines [or bis(oxazolines)] are useful in surface coatings and for molding plastics.[288]

The reaction products of soybean oil, maleic anhydride, and 2-alkenyl-2-oxazolines are useful as plasticizers, lube-oil additives, and as surface coatings.[289]

Low-molecular-weight oxazolines, such as 2-methyl- to 2-heptyl-2-oxazolines, are useful as solvents and plasticizers for resins and, when polymerized, are useful in forming fibers, films, and molded objects.[33,34]

Poly(2-oxazolines) are useful in the preparation of coatings and injection-molded articles. The polymers may be obtained from the polymerization of 2-methyl-2-oxazoline and 2-chloromethyl-2-oxazoline using an oxazolinium perchlorate catalyst.[290]

4-Amino-3-oxazolines having halogenated hydrocarbon substituents in the 2 and 5 positions may be used to modify the film-forming properties of polymethacrylates. An example of an oxazoline for this use is 4-amino-2,2,5,5-tetrakis-(trifluoromethyl)-3-oxazoline.[187]

Out of a series of 25 oxazolines tested for effectiveness as ultraviolet absorbers in clear exterior finishes, 2-(2-hydroxy-5-chlorophenyl)-4,4-bis(hydroxymethyl)-2-oxazoline, 2-(2,6-dihydroxyphenyl)-4,4-bis(hydroxymethyl)-2-oxazoline, 2-(*o*-hydroxyphenyl)-2-oxazoline, 2-(2-hydroxy-1-naphthyl)-4,4-bis(hydroxymethyl)-2-oxazoline, 2-(2,6-dimethoxyphenyl)-4-ethyl-2-oxazoline, 2-(*m*-nitrophenyl)-4-ethyl-2-oxazoline, and 2-(*p*-nitrophenyl)-4-ethyl-2-oxazoline had the best absorption characteristics between 300 and 400 mμ, the region of ultraviolet degradation.[291]

The reaction product from 2-heptadecadienyl-4,4-bis-(hydroxymethyl)-2-oxazoline, trimellitic anhydride, and phthalic anhydride may be used as binders in water-thinned semigloss paints.[239]

B. SURFACE ACTIVE AGENTS

The surface tension of amides, oxazolines, and ester amines derived from the same fatty acids and amino alcohols has been compared. That of an amide is lower than an oxazoline, while the ester amine is much higher.[26]

Oxazolines derived from long-chain fatty acids and amino alcohols have been used to lower the surface tension of mustard gas and the interfacial tension between mustard gas and water.[292]

Organic acid salts of long-chain 2-oxazolines are good cationic surfactants in aqueous systems, with the lauric acid salt being superior to lactic, tartaric, or citric salts.[293]

Surface active compositions containing 2-substituted-4,4-substituted-2-oxazolines are used as a lubricant and freeing agent between well-drilling pipes and well solids.[294]

Reaction products of long-chain 2-oxazolines and acrylic compounds have been used as their sodium salts as detergents and corrosion inhibitors.[219]

Hydroxypolyalkylene ethers of hydroxyalkyl-substituted 2-oxazolines are useful as surface active agents for dispersing pigments in aqueous systems.[252,295]

Long-chain 2-alkyl-2-oxazolines are useful for dispersing pigments in transfer or carbon-paper inks.[296]

Oxazolines prepared from the reaction of carboxylic phenol–aldehyde resins with amino alcohols are useful in the preparation of deemulsifying agents for water-in-oil emulsions.[297]

C. GASOLINE AND LUBE OIL ADDITIVES

The addition of substituted oxazolines, such as 2-heptadec-

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(297) M. DeGroote, U. S. Patent 2,819,250 (1958); *Chem. Abstr.*, **54**, 11059 (1960).

enyl-4,4-bis(hydroxymethyl)-2-oxazoline, to gasoline reduces surface ignition and carburetor fouling and icing.[298,299]

The reaction products of substituted oxazolines, such as 2-heptadecenyl-4,4-bis(hydroxymethyl)-2-oxazoline, and boric acid give improved carburetor cleanliness, act as anti-icing agents, and suppress surface ignition when added to gasoline.[300-305]

Reaction products of oxazolines with phosphite diesters have been used as anti-icing and antiknock additives for fuels.[306,307]

Lubricating greases containing 2-heptyl-4-hydroxymethyl-4-ethyl-2-oxazoline have been used to improve oxidation and corrosion characteristics.[308]

Polymers of low-molecular-weight vinyloxazolines act as dispersants for impurities in lubricating oils, as pour point depressors, and as viscosity index improvers.[118]

Mercaptooxazolines of the type 2-mercapto-4-hydroxymethyl-4-methyl-2-oxazoline are effective corrosion inhibitors in lubricating oils.[309]

D. CORROSION INHIBITORS

Oil-soluble oxazolines, in combination with organic phosphates and sulfonate salts, are effective as rust inhibitors when added to oils. The combination of 2-heptadecenyl-4,4-dimethyl-2-oxazoline and dilauryl phosphate with sodium petroleum sulfonate prevents steel from rusting in humid atmosphere or salt water.[310,311]

Products having excellent inhibiting action on the corrosion of metals may be obtained by treating an oxazoline of the type 2-alkenyl- or 2-alkyl-2-oxazolines with CrO_3.[312]

Organic acid salts of certain oxazolines form a corrosion-preventive film on metals. The salts of ricinoleic acid are the most effective.[313]

Corrosion in wells producing oil–brine mixtures is reduced by the addition of an imidazoline–oxazoline compound prepared from a dibasic acid, a diamine, and an amino alcohol.[314]

The reaction of an amino alcohol, dimerized linoleic acid, and P_2S_5 gives a thiazoline–oxazoline compound which is effective in reducing corrosion of metal in oil production and transmission equipment.[315,316]

Bis(oxazolines), obtained from amino alcohols and dibasic acids, are excellent corrosion inhibitors for steel in brine solutions. As low as 50 ppm provides 99.5% protection, as determined by weight loss.[317]

2-Mercaptooxazolines are useful in detergents containing polyphosphates to prevent tarnishing of metals such as German silver.[318]

Substituted 2-oxazolines in mineral oil at a concentration of 100 ppm effectively prevent corrosion of ferrous metals in the presence of water. Both 2-heptadecenyl- and 2-heptadecyl-4,4-bis(hydroxymethyl)-2-oxazoline give complete protection in static tests.[319]

The use of 2-(2-ethylpentyl)-2-oxazoline has been effective in inhibiting rusting of treated steel surfaces kept in storage prior to electroplating, painting, or hot dip coating.[320]

E. ANTIFOAM AGENTS

Oxazolines are effective antifoam agents and have been used to control foaming during fermentation. The substituted oxazolines having a C_7 to C_{17} group in the 2 position are the most active.[321]

2-Heptadecenyl-4-methyl-4-hydroxymethyl-2-oxazoline has been used to control foaming during the regeneration of amine solutions, which are used for removal of H_2S and CO_2 from synthesis gas.[322]

F. TEXTILE CHEMICALS

A mixture of 2-heptadecenyl-4-methyl-4-hydroxymethyl-2-oxazoline, mineral oil, neatsfoot oil, and oleic–lactic acid amide is a good lubricating and conditioning agent for yarns and fibers.[323]

A good textile lubricant having antistatic properties can be prepared using a mixture of 2-alkyl-4,4-dimethyl-2-oxazoline, mineral oil, phoshate ester of lauric acid, and lauryl alcohol.[324]

Alkylated or acylated oxazolines in combination with hydroxymethylurea compounds give improved creaseproofing to the ureas and provide a softening effect on textiles. It also provides improved shrinkage and wear resistance.[325]

2-Alkyloxazolines which contain a polyglycol ether group in the 4 position are effective in inhibiting swelling of textile

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fibers. For example, the addition of 20 mol of ethylene oxide on 2-undecyl-4-methyl-4-hydroxymethyl-2-oxazoline gives a product which is useful in treating a viscose spinning bath to provide fibers with good physical properties, including improved leveling for dyeing.[326,327]

A variety of aminomethyloxazolines are useful in treating fabric to improve softness during laundering, in treating vinyl acetate and acrylic polymers to improve film-forming properties, as cross-linking agents, and to improve adhesion of polycaproamide yarn toward rubber.[328]

Halogenated oxazolines, such as 2-tribromomethyl-2-oxazoline, are effective as flame retardants in plastics.[77] Also, 2,2,5,5-tetrakis(trifluoromethyl)-4-ethoxy-3-oxazoline has been recommended as a flame-proofing agent and to render paper and fabric oil and water repellant.[185,186]

Oxazoline diesters of saturated long-chain fatty acids are useful for treating cellulose fabric to give durable water repellency. The oxazolines may be made reactive to cellulose by addition of formaldehyde, or they may be used in combination with other reactive resins. The oxazoline diester 2-heptadecyl-4,4-bis(stearoyloxymethyl)-2-oxazoline is quite effective in this application.[329,330]

2-Perfluoroalkyl-2-oxazolines are excellent oil-proofing and soil-resistant agents for textiles. The compound 2-perfluoroheptyl-4,4-dimethyl-2-oxazoline is useful *per se*, or it can be reacted with formaldehyde to form the vinyloxazoline and then polymerized on fabric.[74]

2-Alkyl-2-oxazolines are effective antistatic agents for polypropylene compositions.[331]

Polymers of 2-substituted-2-oxazolines, such as 2-(5-acetoxypentyl)-2-oxazoline, are useful as adhesives, coatings, and impregnants for paper and textiles,[35,230]

Oxazolines are useful in the preparation of linear polymers which can be drawn into fibers which remain elastic at room temperature.[222] Also, treatment of a bis(oxazoline) with dibasic acid gives poly(ester amides) which are useful in production of fibers and plastics. Adipic acid and 2,2′-ethylenebis-(2-oxazoline) have been used in forming polymers for this use.[332]

Glass fibers treated with certain substituted 2-oxazolines and bound together with phenolic binder are prevented from adsorption of moisture without increasing the rate of ion migration from the fiber. Recommended oxazolines include 2-heptadecyl-4,4-bis(hydroxymethyl)-2-oxazoline.[333,334]

G. PHARMACEUTICALS

Substituted 2-oxazolines have been investigated widely for phamaceutical uses. Especially useful as tranquilizing agents and central nervous system regulators are the substituted 2-amino-2-oxazolines. 2-(1-Naphthylamino)-2-oxazoline, substituted and unsubstituted benzofuranylamino-2-oxazolines, and substituted and unsubstituted 2-(1-indanylamino)-2-oxazolines are among those investigated and found useful. Also, 2-(9-fluorenylamino)-2-oxazolines and their salts are effective in the same application.[93,94,103,335]

N-Substituted 2-amino-2-oxazolines in which the substituted group is benzyl, 1-naphthyl, or 1-naphthylmethyl have been tested in dogs and found to have vasoconstrictive properties. The benzylaminooxazoline has 50% of the vasoconstrictive action of adrenaline. N-Substituted aminooxazolines in which the substituent is *o*-tolyl, *p*-tolyl, 2,6-dimethylphenyl, and 2-methyl-6-chlorophenyl have marked vasoconstrictor action and are superior to cocaine in local anesthetic activity.[99,100,336–340]

Aminooxazolines, such as 2-amino-5-phenyl-2-oxazoline, have been tested and found very potent in suppressing appetite. These compounds also cause central nervous system stimulation.[106,107,341–346] Also, *cis*-2-amino-4-methyl-5-phenyl-2-oxazoline has been tested in dogs and found to produce sympathomimetic cardiovascular effects.[347]

Certain oxazolines substituted in the 2 position are competitive inhibitors of acetylcholinesterase. These include 2-amino-2-oxazoline, 2-(1-naphthylamino)-2-oxazoline, and 2-methyl-2-oxazoline.[348]

2-(1-Naphthylamino)-2-oxazoline has a strong sedative action in white mice and 2-(4-methoxy-1-naphthylamino)-2-oxazoline at first produces excitation and then deep sleep.[349]

Partially reduced 2-(1-naphthylamino)-2-oxazolines show antihypertensive and central nervous system depressant activity and have low toxicity.[103]

Substituted arylamino-2-oxazolines, for example, 2-phenylamino-2-oxazolines, are useful in raising blood sugar levels, and exhibit local anesthetic, sedative, vasoconstrictor, blood pressure depressant, and gastric fluid secretion inhibitory effects.[350–352]

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Substituted oxazolines of a slightly different type, for example, 2-(2-hydroxyphenyl)-4,4-bis(hydroxymethyl)-2-oxazoline, are pharmaceutically useful and their salts are active central nervous system depressants.[6,353]

Alkyl-substituted oxazolines are effective antimicrobials. 2-Methyl-2-oxazoline, used in solution or spray form, is especially effective against *Staphylococcus aureus*.[354]

Other substituted oxazolines of interest as antibacterial agents include 2-ethyl-4,4-dimethyl-2-oxazoline, 2-(1-methyl-2-hydroxylethyl)-4,4-dimethyl-2-oxazoline, and 2-(2-phenyl-1-methylethenyl)-4,4-dimethyl-2-oxazoline.[355]

D-*threo*-2-Dichloromethyl-4-(*p*-nitrophenylhydroxymethyl)-2-oxazoline has been tested in mice and found to be transformed into chloramphenicol with a bacteriostatic effect comparable to that antibiotic and an acute toxicity three times smaller than that of chloramphenicol.[150,356]

In a study of several chloramphenicol analogs, L-ψ-2-(dichloromethyl)-5-(*p*-nitrophenyl)-4-hydroxymethyl-2-oxazoline was rated at one-fourth the activity of chloramphenicol against Gram-positive and Gram-negative bacteria.[357]

The activity of D-2-(dichloromethyl)-5-(*p*-nitrophenyl)-4-hydroxymethyl-2-oxazoline against Rocky Mountain spotted fever has been reported. When incorporated in the diet of guinea pigs at levels of 100–500 mg/day, it caused clinical suppression of the disease with development of immunity.[358]

A series of 3-oxazolines has been studied for pharamacological properties. When substituted in the 2 position with long aliphatic chains, they show analgesic properties. When the 2-substituted group is n-C_7H_{15}, the compound has strong sedative effect. Some of the compounds show stimulation and depression of the central nervous system.[188]

2-Mercapto-2-oxazoline has been tested as an antithyroid compound and reported to be three-fourths as active as thiouracil.[359]

Three quaternary oxazolinium compounds, 2-(1-naphthyl)-, 2-(4-methoxyphenyl)-, and 2-(*p*-tolyl)-3-methyl-5-phenyl-2-oxazolinium 4-toluenesulfonate, have been tested in cats and found to cause hypothermia and hypotension proportional to the dose, without affecting respiration or the electrocardiogram. They show no adrenergic or ganglion-blocking properties and do not block the action of acetylcholine or histamine on the isolated intestine.[360]

Some vinyloxazolines, such as 2-isopropenyl-4,4-dimethyl-2-oxazoline, are claimed to be effective fungicides. Also, 2-(9-decenyl)-4,4-dimethyl-2-oxazoline is reported to be at least ten times more effective against bacteria and fungi than 10-undecylenic acid, which is an established fungicide.[119,361]

2-(5-Nitrofuryl)-4-hydroxymethyl-5-(*p*-nitrophenyl)-2-oxazoline has been evaluated and found effective as a trichomonicide.[362]

H. ADHESIVES AND BINDERS

Oxazolines having a long-chain unsaturated group with a vinyl group on the α-carbon and attached at the 2 position of the oxazoline ring are useful in combination with other vinyl monomers as binders for fiberboard. Recommended oxazolines include 2-[1-(hexadecenyl)ethenyl]-4,4-dimethyl-2-oxazoline.[363]

Long-chain oxazolines, such as 2-heptadecyl-4,4-bis(hydroxymethyl)-2-oxazoline, are effective as antistripping agents in asphalt pavings.[364,365]

Polymerized 2-isopropenyl-2-oxazoline gives improved adhesion of tire cords to rubber compositions.[366]

Oxazoline esters of the type 2-alkyl-4-methyl-4-acyloxymethyl-2-oxazoline are good plasticizers prior to vulcanization of butadiene–acrylonitrile rubber.

Also, bis(oxazolines), such as 2,2′-tetramethylenebis(4,4-dimethyl-2-oxazoline), give improved properties when used as vulcanizing agents for rubber.[127,367,368]

I. STABILIZERS FOR CHLORINATED HYDROCARBONS

Chlorinated hydrocarbons may be stabilized against metal-induced decomposition by the addition of a small amount of an oxazoline, such as 2-methyl-2-oxazoline.[369] 2-Ethoxy-2-oxazoline, at 0.02% concentration, is a good stabilizer for trichloroethylene.[48]

Vinyl chloride resins are stabilized by the addition of substituted 2-oxazolines, such as 2-ethyl-4,4-dimethyl-2-oxazoline. The resin is protected from heat degradation when applied on metal surfaces.[370]

The presence of a small amount of vinyloxazoline copolymerized with vinyl chloride gives thermal stability to the polymer. Vinyl chloride, vinyl acetate, and 2-isopropenyl-4-ethyl-4-propionyloxymethyl-2-oxazoline gives a terpolymer having excellent heat stability when applied on steel surfaces.[371]

J. STABILIZERS FOR AQUEOUS FORMALDEHYDE SOLUTIONS

Aqueous formaldehyde solutions can be stabilized against polymer formation by the addition of an oxazoline of the

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type 2,4,4-trimethyl-2-oxazoline or 2-methyl-4,4-bis(hydroxymethyl)-2-oxazoline.[372]

Epoxide addition products of hydroxymethyl-substituted oxazolines have also been effective in stabilizing formaldehyde solutions. For example, 2-heptadecenyl-4,4-bis(2-hydroxyethoxymethyl)-2-oxazoline at a concentration of only 50 ppm will stabilize 44% formaldehyde against polymer formation.[373]

K. PROTECTIVE FILMS IN POLISH FORMULATIONS

Oxazoline diester waxes prepared from 2-amino-2-hydroxymethyl-1,3-propanediol and saturated fatty acids have been used in polish formulations. In addition to good properties as a protective film, the waxes contribute mildew and fungus resistance, and antistatic and anticorrosive properties.[374,375]

L. FOAM STABILIZERS

Foam stability of detergents is improved by addition of 2-alkyl-4,4-bis(hydroxymethyl)-2-oxazolines. Alkyl groups of C_9 to C_{13} are effective, with 2-hendecyl-4,4-bis(hydroxymethyl)-2-oxazoline giving best results.[376]

M. PHOTOGRAPHY

The addition of 2-mercapto-2-oxazolines (or substituted derivatives) to photoinsensitive, image-receptive coatings containing colloidal silver causes the formation of a darker positive image.[377-380] 2-Mercapto-2-oxazolines are also used in photography as antifoggant development retarders.[381,382]

Photographic sensitizers have been prepared which contain substituted 2-oxazolines, such as 2,4-dimethyl-4-acetoxymethyl-2-oxazoline.[383]

N. AGRICULTURE

A study of phytotoxicity of a series of 2-substituted-4-methyl-4-hydroxymethyl-2-oxazolines has shown that the substitution of one or more OH groups for hydrogen atoms in the methyl group markedly reduces toxicity. Compounds with short-chain alkyl groups in the 2 position are less toxic than those with longer groups in that position. The presence of one or more double bonds in the chain increases toxicity.[384]

Aromatic imido esters prepared by treating substituted oxazolines with phthalic or naphthalic anhydride have been suggested as plant growth regulators.[385]

Formulations of 2-ethylthio-2-oxazoline or 2-propargylthio-2-oxazoline are effective in controlling plant-infesting nematodes.[386-388]

O. PLASTICIZERS

Long-chain oxazolines or ethylene oxide addition products of long-chain oxazolines, such as 2-heptadecenyl-4-methyl-4-hydroxymethyl-2-oxazoline or 2-heptadecenyl-4-methyl-4-hydroxydiethoxymethyl-2-oxazoline, have been used to improve plasticity and extrudability of gelatin dynamite compositions.[389]

Reaction products of nitro alcohols and substituted 2-oxazolines are useful as plasticizers for nitrocellulose.[268]

Succinimido esters prepared from succinic anhydride and 2-alkyl- or 2-alkenyl-2-oxazoline are useful as plasticizers when the group in the 2 position is a long chain.[390]

2-Perfluoroalkyl-2-oxazolines, for example 2-pentadecafluoroheptyl-2-oxazoline, have been recommended for use as plasticizers for resins.[75]

V. Analytical

An analytical method of value in determining purity of oxazolines is the nonaqueous titration in glacial acetic acid, using about 0.1 N $HClO_4$ in acetic acid as titrant.[391]

Oxazolines which contain a hydroxymethyl group in the 4 position are quantitatively oxidized by HIO_4 in aqueous solution, making possible the use of this reaction as an analytical procedure.[392,393] Also, a chromatographic method has been developed which has good sensitivity for oxazolines.[394]

Nuclear magnetic resonance parameters of 2-methyl-2-oxazoline, 2,4,4-trimethyl-2-oxazoline, and 2,5,5-trimethyl-2-oxazoline have been reported. The variation with pH of the methyl proton shift has been used in determining the pK_a of 2-methyl-2-oxazoline.[395]

Nuclear magnetic resonance has been used to follow decomposition of aqueous solutions of 2-methyl-2-oxazoline at constant pH values in the range −1 to 14. Decomposition is first order with respect to total oxazoline at any pH, but

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deviates from the simple reaction of water with the protonated species above pH 5.[396]

Infrared and proton magnetic resonance spectra have been used to show that the double bond of 2-amino-5-aryl-4-methyl-2-oxazolines is endocyclic regardless of the substituent on the amino group.[397]

Infrared spectra have been reported for some substituted 2-oxazolines, such as 2,4- and 2,5-dimethyl-2-oxazolines.[398]

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