# THE CHEMISTRY OF THE OXAZOLINES

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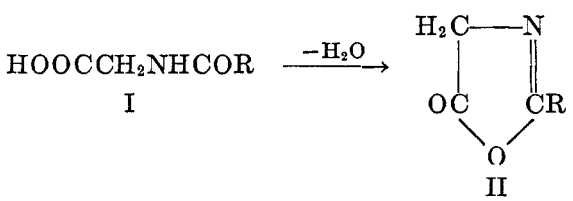
CONTENTS



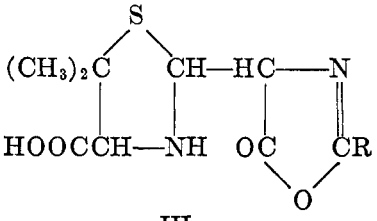
## I. INTRODUCTION

The oxazolines, or dihydroöxazoles, are of interest because of the close relation between the acyl derivatives of α-amino acids (I) and the 5-keto-2-oxazolines (II).



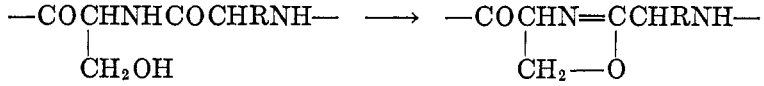

I II

The Erlenmeyer azlactone synthesis of amino acids (21), the formal possibility of the existence of oxazoline rings in polypeptides (7, 89), the azlactone penicillin possibility (III) (24a, 81a), and the use of azlactones in building up chains



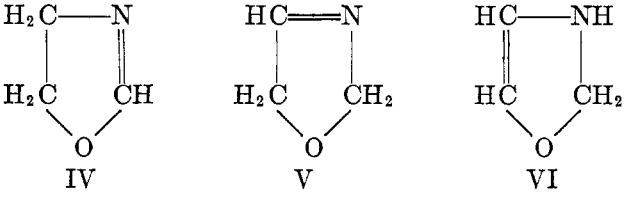
III

with peptide linkages (6a) are all manifestations of this relation. Other interests in the oxazolines have also been developed. The formation of an oxazoline ring through cyclodehydration at peptide linkages formed from the $\alpha$-amino-$\beta$-hydroxy acids, serine or threonine, has been postulated by Blackburn and others (13).



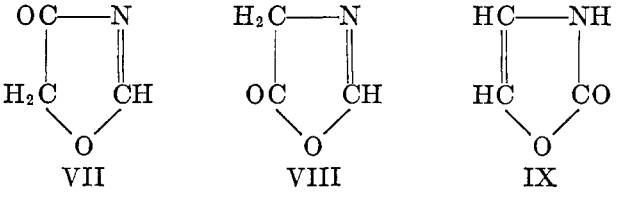
The 2-oxazolines, available from *N*-acyl derivatives of ethanolamine, have been used as cationic surface-active agents. Analogies drawn from the relation between procaine and 2-oxazolines have been used in designing local anesthetics (1, 53). One oxazoline has been reportedly isolated from a Canadian weed (42). Synthetic anhydrides of acylserines (7) and other peptides (40, 76) have been studied.

There are three possible types of oxazoline or dihydroöxazole: 2-oxazoline (IV), 3-oxazoline (V), and 4-oxazoline (VI).



IV V VI

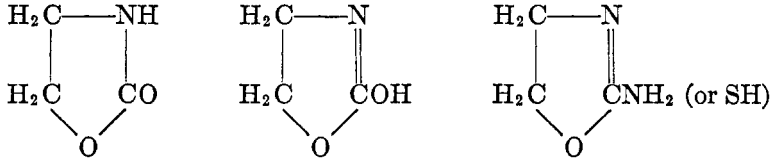
2-Oxazolines (IV) and their derivatives are by far the most common. Very little is known about the 3- and 4-oxazolines. Ketoöxazolines (VII, VIII, IX), in which a carbonyl replaces a methylene group, derived from 2- and 4-oxazolines are known, but those from 3-oxazolines are not known.[1] The 5-keto-2-oxazolines



VII VIII IX

[1] *Note added in proof:* Compounds of this type are reported in *The Chemistry of Penicillin*, Princeton University Press, 1949, pp. 739–42, where they are called pseudoxazolones.

(VIII) or azlactones, the intermediates in the Erlenmeyer azlactone synthesis of amino acids, have been reviewed by Carter (21) and only recent developments will be included here.[2] Some oxazolidones, where the carbonyl is on a carbon adjacent to an NH group as in X, are hydroxyoxazolines in their enolic forms (XI). These belong properly with a discussion of other oxazolidones and are not included here. The 2-amino(or mercapto)-2-oxazolines (XII) are included in separate sections of this discussion. The oxidoöxazoles (which are 4,5-epoxy-oxazolines) and the 2-aminoöxazoles (or 2-imino-2-oxazolines) have been discussed elsewhere (89).




Historically, the first oxazoline was prepared in 1884 by Andreasch (2). He suspected that the compound resulting from the dehydrohalogenation of allylurea bromide contained a new cyclic structure, but failed to deduce its correct formula. Gabriel five years later (32) first recognized an oxazoline as such and began an extensive study of the chemistry of this heterocyclic system. The present review has been prepared to analyze the available information on the oxazoline types and to indicate portions of the field for which little or no information is available.

## II. 2-Oxazolines

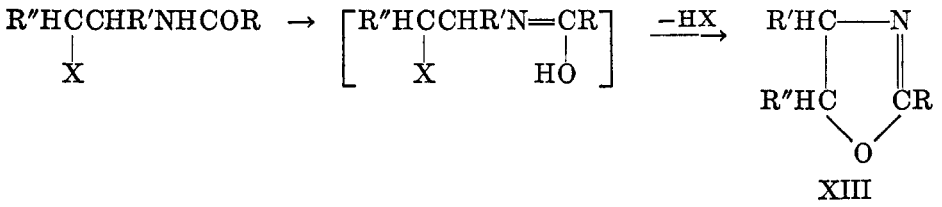
### A. Syntheses of 2-oxazolines

The known syntheses for 2-oxazolines follow the usual pattern for the formation of cyclic compounds. The ring is formed by a condensation reaction in which the elements of water or halogen acid are removed from a suitable open-chain compound. Examples of the types used are *N*-acyl derivatives of β-halo- and β-hydroxy-alkylamines and iminoesters of β-halo- or β-hydroxy-amines. A few types of substituted 2-oxazolines are also available by cyclization reactions from modified amides. Thus, β-halo- and β-hydroxy-alkylureas form 2-amino-2-oxazolines, and acylamino acids form the azlactones or 5-keto-2-oxazolines. 2-Mercapto types are available directly from carbon bisulfide and ethanolamines. These, and other syntheses, are discussed in this and following sections.

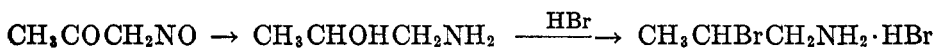
#### *1. From β-haloalkylamides*

The synthesis of 2-oxazolines from β-haloalkylamides has been the most widely used method for preparing these compounds. The reaction takes place according to the following equation:

[2] *Note added in proof:* These compounds are also surveyed in *The Chemistry of Penicillin*, Princeton University Press, 1949.



The various 2-oxazolines prepared by this method are listed in table 1. R in XIII, which is derived from the acyl group, has been varied widely but in most reported 2-oxazolines is aryl. Variations in R′ and R″ in XIII are very few, since only a few β-haloamines are available. In all but a few 2-oxazolines, R′ is H and R″ is H or $CH_3$. These are derived from β-haloethyl- or β-halopropyl-amines. The former is readily available from ethanolamine; the latter from allylamine and hydrogen bromide (25) or from nitrosoacetone as follows (73):



β-Chloro-*n*-butylamine, from which a 2-oxazoline with R″ an ethyl group is obtained, has been prepared by Bookman (15). Since the haloamines are usually prepared from hydroxyamines, which can themselves be converted to oxazolines, the haloamide method is not as direct as is the synthesis from hydroxyamides described in the next section.

In most instances the dehydrohalogenation has been effected by heating the β-haloamide with aqueous or alcoholic alkali; acetic anhydride has been used, but yields are low (33, 36). The oxazoline is easily isolated and purified. A typical preparation is that used by Gabriel and Heymann (36) for 2-phenyl-2-oxazoline. One mole of bromoethylbenzamide is dissolved as quickly as possible in hot water and 1 mole of sodium hydroxide added; an oil separates which is steam distilled, extracted with ether, and purified by distillation. It was this method that Wenker (86) used in preparing unsubstituted 2-oxazoline from β-chloroethylformamide, and 2,2′-$\Delta^2$-dioxazoline from di-β-chloroethyloxamide.

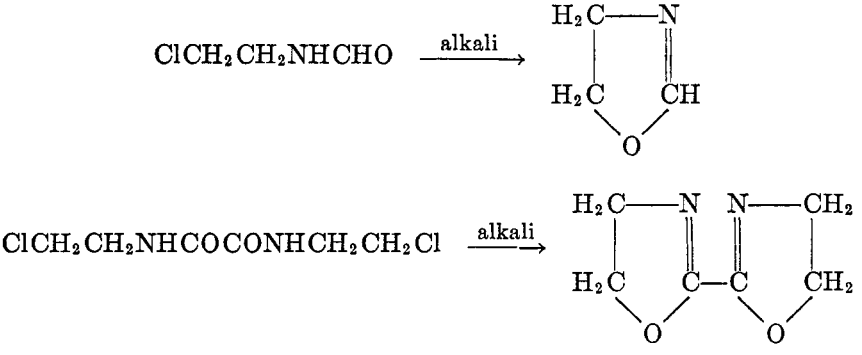
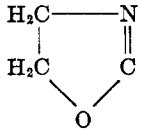


TABLE 1

*2-Oxazolines from β-haloalkylamides*

| SUBSTITUENTS IN 2-OXAZOLINE* | | | YIELD† | REFERENCE |
|---|---|---|---|---|
| R | R′ | R″ | | |
| | | | *per cent* | |
| H | H | H | 39 | (86) |
| $CH_3$ | H | H | 40 | (33, 35, 36) |
| $C_6H_5$ | H | H | 50 | (36) |
| $p$-$CH_3C_6H_4$ | H | H | 75 | (66) |
| $o$-$CH_3C_6H_4$ | H | H | 50 | (66) |
| $C_6H_5CH_2$ | H | H | Poor | (25) |
| $m$-$NO_2C_6H_4$ | H | H | 82 | (25, 53) |
| $o$-$NO_2C_6H_4$ | H | H | 92 | (53) |
| $p$-$NO_2C_6H_4$ | H | H | 72 | (53) |
| $p$-$ClC_6H_4CH_2$ | H | H | 93 | (53) |
| β-$C_{10}H_7$ | H | H | | (67) |
| α-$C_{10}H_7$ | H | H | | (67) |
| $p$-$CH_3OC_6H_4$ | H | H | | (62) |
| $p$-$C_2H_5OC_6H_4$ | H | H | | (26) |
| $p$-$C_4H_9OC_6H_4$ | H | H | | (26) |
| $m$-$NO_2$-$p$-$CH_3OC_6H_3$ | H | H | 91 | (53) |
| $m$-$NO_2C_6H_4CH{=}CH$ | H | H | 75 | (53) |
|  | H | H | 84 | (86) |
| $C_6H_5$ | $C_6H_5$ | H | | (34) |
| $p$-$NO_2C_6H_4$ | $C_4H_9$ | H | 43 | (53) |
| $p$-$NO_2C_6H_4$ | $C_6H_5$ | H | 86 | (53) |
| $CH_3$ | H | $CH_3$ | 15 | (79) |
| $C_6H_5$ | H | $CH_3$ | 60–66 | (36, 79) |
| $C_6H_5$ | H | $C_2H_5$ | | (15) |
| $C_6H_5CH_2$ | H | $CH_3$ | Poor | (25) |
| $C_6H_5CH{=}CH$ | H | $CH_3$ | 60 | (25) |
| $C_6H_5$ | H | $C_6H_5$ | | (91) |
| $o$-$C_6H_4CH_3$ | H | $CH_3$ | 65 | (66) |
| $p$-$C_6H_4CH_3$ | H | $CH_3$ | | (66) |
| $o$-$C_6H_4NO_2$ | H | $CH_3$ | 83 | (53, 79) |
| $p$-$C_6H_4NO_2$ | H | $CH_3$ | 91 | (53, 79) |
| $m$-$C_6H_4NO_2$ | H | $CH_3$ | 93 | (25, 53) |
| α-$C_{10}H_7$ | H | $CH_3$ | | (67) |
| β-$C_{10}H_7$ | H | $CH_3$ | | (67) |
| $C_6H_5$ | $CH_3$ | $CH_3$ | | (73) |
| $p$-$C_6H_4NO_2$ | $CH_3$ | $CH_3$ | 74 | (53) |
| $C_6H_5$ | $CH_3$ | $C_2H_5$ | | (44) |

* R, R′, R″ of formula XIII.

† Where there is more than one reference, only the best yield is given.

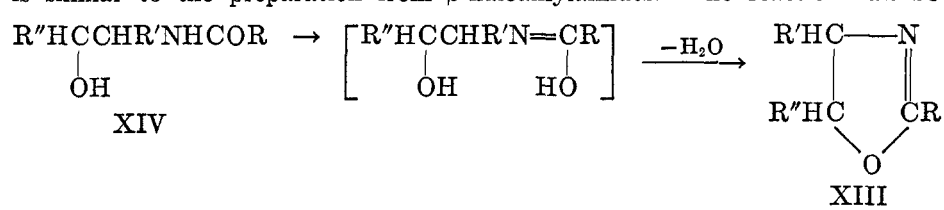
TABLE 2

*Oxazolines from β-hydroxyalkylamides*

| SUBSTITUENTS IN 2-OXAZOLINE | | | YIELD | REFERENCE |
|---|---|---|---|---|
| In 2-position | In 4-position | In 5-position | | |
| | | | *per cent* | |
| $CH_3$ | H | H | 30 | (85) |
| $C_2H_5$ | H | H | 35 | (85) |
| $C_6H_5$ | H | H | 22 | (85) |
| $CH_3(CH_2)_{10}$ | H | $ClCH_2$ | | (8) |
| $C_6H_5$ | H | $C_6H_5$ | | (74) |
| $C_6H_5$ | H | $C_6H_5COOCH_2$ | | (4) |
| $C_6H_5$ | H | $ClCH_2$ | | (3) |
| $C_6H_5$ | H | $ClCOCH_2$ | | (6) |
| $C_6H_5$ | H | $C_2H_5OCOCH_2$ | | (6) |
| $p$-$NO_2C_6H_4$ | H | $ClCH_2$ | 88 | (53) |
| $p$-$NO_2C_6H_4$ | H | $(C_2H_5)_2NCH_2$ | 86 | (53) |
| $p$-$NO_2C_6H_4$ | H | $(C_4H_9)_2NCH_2$ | 97 | (53) |
| $C_6H_5$ | H | $CH_3$, $CH_3$ | | (22) |
| $C_6H_5$ | H | $C_6H_5$, $CH_3$ | 95 | (51) |
| $m$-$NO_2C_6H_4$ | H | $CH_3$, $CH_3$ | 95 | (53) |
| $p$-$NO_2C_6H_4$ | H | $CH_3$, $CH_3$ | 86 | (53) |
| $C_6H_5$ | $CH_3OCO$ | H | | (7) |
| $CH_3$ | $CH_3$, $CH_3$ | H | | (77) |
| $CH_3$ | $HOCH_2$, $HOCH_2$ | H | | (79a) |
| $CH_3$ | $CH_3$, $CH_3COOCH_2$ | H | | (77) |
| $CH_3$ | $CH_3COOCH_2$, $CH_3COOCH_2$ | H | | (77, 78) |
| $C_{11}H_{23}$ | $CH_3$, $CH_3$ | H | | (77) |
| $C_6H_5$ | $CH_3$, $HOCH_2$ | H | 67 | (10) |
| $C_6H_5$ | $C_2H_5$, $HOCH_2$ | H | 72 | (10) |
| $C_6H_5$ | $HOCH_2$, $HOCH_2$ | H | 60–65 | (10) |
| $C_6H_5$ | $CH_3$, $CH_3$ | H | | (77) |
| $C_6H_5$ | $CH_3$ | $C_6H_5$ | 75 | (61) |
| $CH_3$ | $C_6H_5$ | $C_6H_5$, $C_6H_5$ | | (51) |
| $C_6H_5$ | $CH_3$ | $C_6H_5CH_2$, $C_6H_5CH_2$ | | (9) |
| $p$-$NO_2C_6H_4$ | (4,5-Cyclohexano) | | 38 | (53) |

*2. From β-hydroxyalkylamides*

The preparation of 2-oxazolines by the dehydration of β-hydroxyalkylamides is similar to the preparation from β-haloalkylamides. The reaction can be




visualized as a cyclodehydration of the imido form of an amide of a β-hydroxyalkylamine. The 2-oxazolines prepared by this method are listed in table 2. β-Hydroxyamides are available from amines prepared in turn from chlorohydrins

on reaction with ammonia; or via the Gabriel primary amine synthesis (22); or from the condensation of aromatic aldehydes with nitroethane (61); or by reduction of cyanohydrins (91). Many types are available and can be used in preparing 2-oxazolines with a variety of substituents. Several examples of oxazolines with two substituents in the 4- or 5-position are known and many types with functional groups as substituents have been prepared. Thus, the glycerol chlorohydrins react with amines to furnish hydroxyamides for synthesis of the hydroxymethyl-substituted types. This method is more direct than the haloamide method, discussed in the preceding section, because the halo derivatives necessary for the preparation of haloamides are usually prepared from hydroxyamines. This probably accounts for the wide variety of 2-oxazolines prepared from hydroxyamides.

Among the dehydrating agents, sulfuric acid (51, 53, 61, 74) and thionyl chloride (4, 7, 53) have been most commonly used; phosphorus oxychloride (4) and phosphorus pentoxide (51, 85) are also effective. In one instance (22) cyclization occurred upon heating with water and cyclization may take place on heating in organic solvents. Thus, Valco (79a) dehydrated the hydroxyamide by boiling in toluene or xylene and distilling out the water–hydrocarbon azeotrope as the water formed.

The mechanism is probably cyclodehydration as indicated above. It might be supposed, however, to involve preliminary dehydration followed by cyclization:

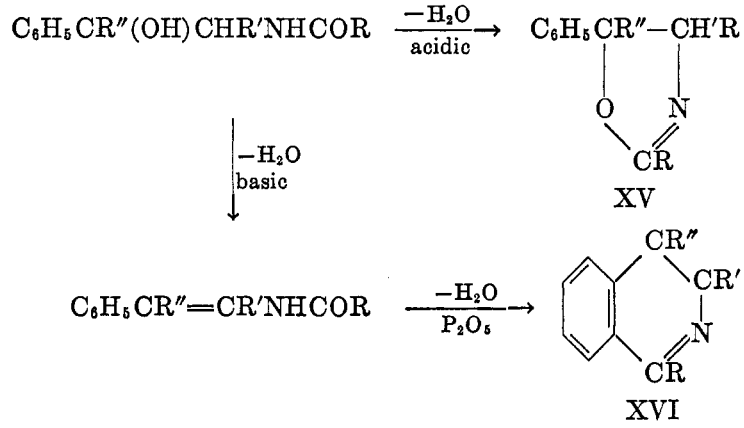
$$\text{XIX} \rightarrow [\text{R''HC}{=}\text{CR'NHCOR}] \rightarrow \text{XIII}$$

This point has not been systematically investigated and there is not sufficient evidence to indicate the course taken by the reaction. Information on this point might be obtained by comparing the yields of oxazoline obtained from unsaturated amides with yields obtained from β-halo- and β-hydroxy-amides. The work of Krabbe *et al.* (51) discussed below suggests that unsaturated amides are not readily converted to oxazolines.

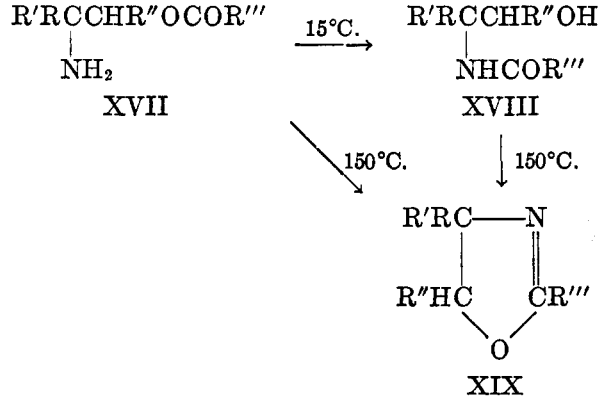
The isolation and purification of the product are simple and straightforward. Typical procedures are those of Leffler and Adams (53), using either thionyl chloride or sulfuric acid. The procedure for the sulfuric acid dehydration is as follows: One hundred cubic centimeters of concentrated sulfuric acid is added to 0.15 mole of β-hydroxy-*p*-nitrobenzamide and the mixture held at 55–60°C. for 10 min. After cooling to 15°C. it is poured into ice water and filtered, and the oxazoline precipitated from the filtrate by adding ammonia. The procedure for the thionyl chloride dehydration is described as follows. Thionyl chloride (33.4 g.) is added to 0.01 mole of γ-diethylamino-β-hydroxypropyl-*p*-nitrobenzamide and the mixture heated on the water bath for 1.5–2 hr. After cooling to 5°C., it is poured into dry ether and allowed to stand overnight. The hydrochloride of the oxazoline separates and is collected on a filter and dissolved in water. The free oxazoline is obtained by making the filtrate alkaline with sodium hydroxide.

In certain β-hydroxyamides containing a β-phenyl substituent there are two possibilities for ring closure to give either the isoquinoline or the oxazoline, de-

pending upon the manner in which the dehydration is carried out. Krabbe *et al.* (51) have found that acidic reagents, such as sulfuric acid, phosphorus pentoxide, or chloroxalic ester, gave the oxazoline (XV), while ethylmagnesium bromide gave exclusively the *N*-acylvinylamine, which could then be converted to the isoquinoline (XVI) with phosphorus pentoxide. Where R″ is phenyl, only the isoquinoline can be formed.




A variation of this method of synthesis uses β-aminoesters (XVII) as starting materials (49, 77). The transformation probably involves migration of the acyl group from oxygen to nitrogen to yield XVIII prior to cyclization to XIX. Such migrations are well-known and will be discussed in a later section.

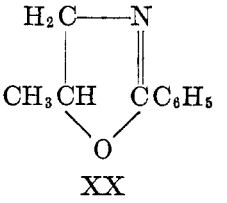



If an amide of the β-aminoester (XVII) is used in place of the aminoester, an acid is split out with the formation of the oxazoline. When R‴ is $CH_3$, R″ is H, and R and R′ are acetoxymethyl groups, 2-methyl-4,4-bis(acetoxymethyl)-2-oxazoline is formed in 67 per cent yield. (78). A series of oxazolines have been prepared from *N*-acyl derivatives of amino sugars by reactions which fall within this class (16, 88, 92, 93).

### *3. From amides of unsaturated amines*

Gabriel and Stelzner (38) observed that *N*-vinylbenzamide was converted to 2-phenyl-2-oxazoline on distillation. This reaction probably involves simple cyclization by an addition reaction. It has also been observed, by Kay (50) and Diels and Beccard (23), that *N*-allylbenzamide is converted to 2-phenyl-5-methyl-2-oxazoline (XX) on heating with concentrated sulfuric or hydrochloric acid. The formation of this product can be explained on the assumption that an intermediate β-hydroxyalkylamide sulfate or β-haloalkylamide is formed by addition of acid to the allyl double bond, followed by cyclization.

$$CH_2{=}CHCH_2NHCOC_6H_5 \rightarrow [CH_3CH(OSO_2OH)CH_2NHCOC_6H_5] \rightarrow$$



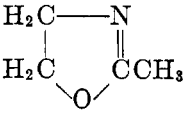
XX

2-*o*-Hydroxyphenyl-5-methyl-2-oxazoline was apparently prepared by this method (23). The type reaction has not been otherwise used, presumably because the unsaturated amides have been available only from β-hydroxy- or β-halo-alkylamides which are themselves readily cyclized to 2-oxazolines. The work of Krabbe *et al.* (51), discussed previously, indicates that *N*-acylvinylamines having two phenyl groups on the β-carbon atom will cyclize to isoquinolines (XVI).

### *4. From iminoesters*

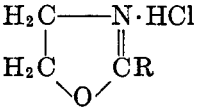
Another route to oxazolines starts with the iminoesters of β-halo- or β-hydroxyamines. Gabriel and Neumann (37) showed that the oxazoline is formed when the iminoester of a β-chloroalcohol is decomposed with sodium hydroxide or in a desiccator over sulfuric acid, but that the *N*-chloroalkylamide product forms when the iminoester is decomposed thermally.

$$CH_3CONHCH_2CH_2Cl \xleftarrow{\text{heat}} CH_3C(NH)OCH_2CH_2Cl \xrightarrow{NaOH}$$



Wislicenus and Körber (90) investigated this conversion more thoroughly and were able to prove that the oxazoline is the intermediate in the migration of an alkyl group from the oxygen in an iminoester to the nitrogen in an amide (XXI).

$$RC(NH)OCH_2CH_2Cl \rightleftarrows$$



$$\rightleftarrows RCONHCH_2CH_2Cl$$

XXI

This equilibrium will be discussed in detail in the section on reactions of 2-oxazolines.

The iminoester method has not been extensively used. A recent modification (54) yields the oxazoline in one step from a nitrile and a β-aminoalcohol. The nitrile and alcohol, with a little sodium methoxide as catalyst, are heated together in a silver-lined vessel until evolution of ammonia has ceased, and the oxazoline is then distilled at reduced pressure from the reaction mixture. 2-[(Ethoxymethoxy)methyl]-2-oxazoline, prepared by this method from ethanolamine and $C_2H_5OCH_2OCH_2CN$, was obtained in 32 per cent yield.

Another variation (14) starts with a β-hydroxyamine and an iminoester. The first step is presumably the formation of a new iminoester, which then cyclizes normally. This method was used by Bockemühl and Knoll (14) in the following

TABLE 3

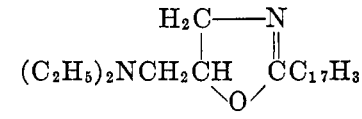
*Boiling and melting points of 2-oxazolines*

| SUBSTITUENTS IN 2-OXAZOLINE | BOILING POINT | MELTING POINT | REFERENCE |
|---|---|---|---|
| | °C. | °C. | |
| | 98 | | (86) |
| 2-Methyl | 109–110/757 mm. | | (35) |
| 2-Phenyl | 242–243 | | (36) |
| 2-*p*-Tolyl | 264–265 | 66 | (66) |
| 2-*o*-Tolyl | 254 | | (66) |
| 2,5-Dimethyl | 117–119 | | (79) |
| 2-Phenyl-5-methyl | 243–244 | | (36) |
| 2,5-Diphenyl | 229–230/44 mm. | | (91) |
| 2,4-Diphenyl | 210/19 mm. | | (34) |

synthesis in which the reaction was carried out in absolute alcohol, the mixture allowed to stand, and the oxazoline obtained by evaporation of the solvent.

$$(C_2H_5)_2NCH_2CHOHCH_2NH_2 + C_{17}H_{35}C(NH)OC_2H_5 \xrightarrow{-NH_3}$$

$$(C_2H_5)_2NCH_2CHOHCH_2N{=}C(OC_2H_5)C_{17}H_{35} \xrightarrow{-C_2H_5OH}$$



## B. PHYSICAL PROPERTIES OF 2-OXAZOLINES

The physical properties of the oxazolines depend significantly upon the nature of the substituents in the ring. The low-molecular-weight members are mobile colorless oils with a sweet, pyridine-like odor. 2-Oxazoline itself boils at 98°C. The effect of introducing substituents of increasing size is shown in table 3. Successful distillation at the boiling points given indicates a fair degree of thermal stability. Spectrochemical data have been reported for 2-phenyl-2-oxazoline (18) and 2,5-diphenyl-2-oxazoline (82).

## C. CHEMICAL PROPERTIES OF 2-OXAZOLINES

The oxazoline ring itself imparts no unusual identity to the oxazolines as a class. They react, in general, about as one would predict that similar functioning groups in open-chain compounds would react. By way of summary it can be said that the 2-oxazolines are typical weak bases, whose lower members dissolve in water to render it alkaline to phenolphthalein. As bases they form the usual salts with acids; these salts vary in stability with the nature of the oxazoline. Quaternary salts are also known. The oxazoline ring is stable towards mild oxidation–reduction or hydrolytic conditions. 2-Phenyl-2-oxazolines can be nitrated and the nitro compound reduced to the amine without rupturing the ring (1, 53). Oxazolines containing a methylol group in the 4-position have been oxidized to oxazoline-4-carboxylic acids (10). Under vigorous conditions, however, the ring readily cleaves. Sodium and alcohol (39) yield a secondary amine. Heating with dilute acid, but apparently not always with dilute alkali, hydrolyzes oxazolines completely. It is noted that no instance of reduction of an oxazoline to an oxazolidine or dehydrogenation to an oxazole has been recorded. Other reactions, discussed in the following sections, provide additional evidence as to the behavior of the functioning groups in the 2-oxazolines.

### *1. Salt formation*

Oxazoline salts of most of the common acid reagents have been reported. The stability of these salts is varied. 2-Oxazoline forms an unstable hydrochloride which spontaneously hydrolyzes to *N*-β-bromoethylformamide, but hydrochlorides of oxazolines of higher molecular weight are stable substances with definite melting points. Many salts have been used for identification of the oxazolines. The salts are of course unstable towards hot water, owing to the ease with which dilute acid hydrolyzes the ring. The properties of these salts are in general similar to those of salts of weak bases.

Only recently and only in two instances (41, 43) has the formation of quaternary oxazoline salts been recorded. Hamer and Rathbone (41) have made the methiodide and ethiodide of 2-methyl-2-oxazoline. The oxazoline reacts exothermally with methyl iodide to produce the quaternary salt as a white deliquescent solid; the corresponding ethiodide, a yellow deliquescent solid, is formed when the oxazoline is heated with ethyl iodide at 100°C. for 4 hr.

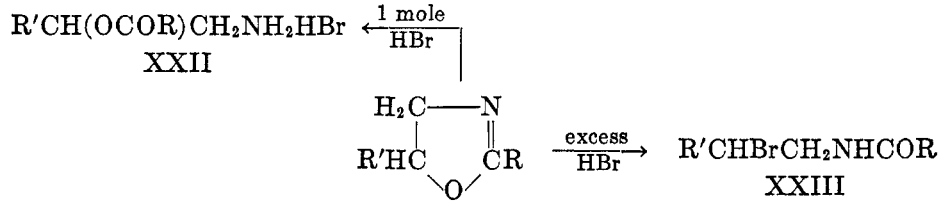
### *2. Hydrolysis*

Oxazolines are not easily hydrolyzed by water, as is evident from the fact that the 2-aryl types are not decomposed when isolated by steam distillation. The importance of the role played by substituents in the nucleus is seen in the fact that Wenker reported (86) that boiling water converts 2-oxazoline to β-hydroxyethylformamide.

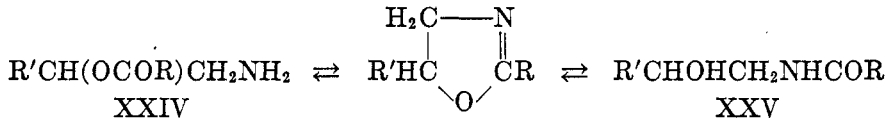
From the method employed for their synthesis, it is evident that oxazolines as a group have considerable stability towards aqueous or alcoholic alkali and such acidic dehydrating agents as thionyl chloride, sulfuric acid, and phosphorus pentoxide. Dilute aqueous acid has no effect on most oxazolines other than salt

formation, but boiling with dilute acid gives an easy hydrolysis. Aqueous alkali can also rupture the ring, although apparently less readily than acid.

Gabriel and Heymann (36) early observed that an oxazoline might be hydrolyzed to a β-aminoester (XXII) with 1 mole of hydrobromic acid or to a β-haloalkylamide (XXIII) with an excess of hydrobromic acid. This reaction was carried out with 2-phenyl-2-oxazoline and 2-phenyl-5-methyl-2-oxazoline. Salomon (66) obtained similar results with 2-*o*-tolyl-2-oxazoline.




Connected with the hydrolysis of oxazolines is the migration of an acyl group from the oxygen of a β-aminoester (XXIV) to the nitrogen of a β-hydroxyamide (XXV) and the reverse reaction. This migration has been frequently observed, and it has been definitely established that the ozaxoline is the intermediate in the transformation.



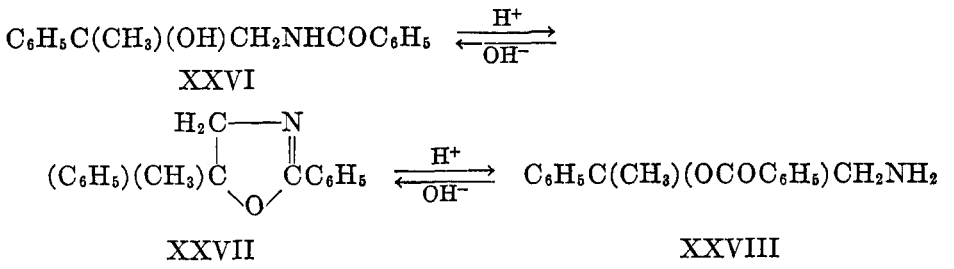

The ease of this migration and the reagents required to effect it depend upon the nature of the compounds. Bettzieche (9), working with benzamides (XXVa)

$$R'_2COHCH_2NHCOC_6H_5$$
XXVa

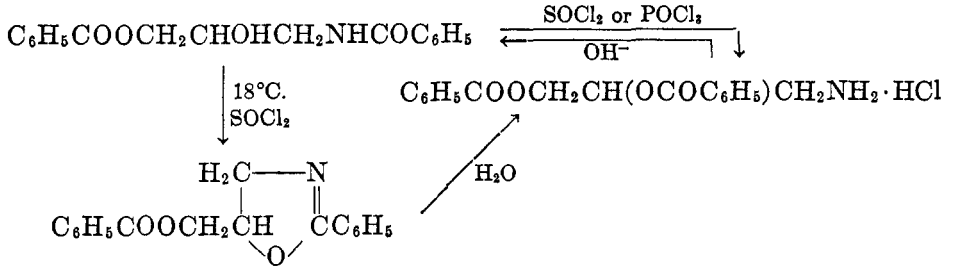
found that sulfuric acid rapidly caused migration from nitrogen to oxygen and quantitatively when R′ is methyl or ethyl. When R′ is benzyl or phenyl, migration was not observed. He also found that migration from oxygen to nitrogen under the influence of alkali was slow and gave mixtures of oxazolines and *N*-acyl compounds. On the other hand, Bergmann and Miekeley (7), in a study of benzoylserine, found that the cycle

*N*-benzoyl → oxazoline → *O*-benzoyl → *N*-benzoyl

could be completed without difficulty. In their studies of amides such as XXVI, Krabbe, Eisenlohr, and Schöne (51) found that they could move from left to right with acid and from right to left with base as indicated. If the oxazoline XXVII is isolated, it can be converted to the *N*-acyl compound (XXVI) with alkali or to the *O*-acyl compound (XXVIII) with acid.



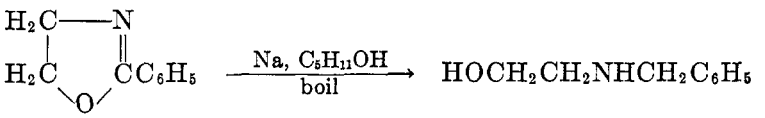

Similar results were obtained by Bergmann and Brand (4), who observed the migrations indicated in the following scheme:




It seems rather well established that the migration is from nitrogen to oxygen in acid and the reverse in alkali. That there may be some misunderstood or variable factors is indicated by the fact, noted in the formation of XXII and XXIII, that some oxazolines can be converted to either the *N*-acyl or *O*-acyl compounds by using hydrobromic acid in varying proportions. A fact of interest in connection with the hydrolytic stability of 2-oxazolines to acids is a ring cleavage in non-aqueous medium. 2,5-Diphenyloxazoline when dissolved in dry ether and treated with hydrogen chloride forms $C_6H_5CHClCH_2NHCOC_6H_5$ (74).

### *3. Reduction*

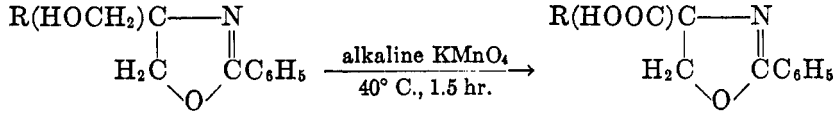
Attempts to reduce 2-oxazolines to oxazolidines using sodium and alcohol lead only to ring cleavage. Thus, with 2-phenyl-2-oxazoline there results *N*-benzylethanolamine (39).




No less vigorous reducing agents have been tried and this information does not indicate whether the 2-oxazoline or the oxazolidine ring is cleaved in the process. The 2-oxazoline ring is stable to mild reducing agents. Leffler and Adams (53) were able to reduce a number of 2-nitrophenyl-2-oxazolines to the corresponding 2-aminophenyl compounds with iron and hydrochloric acid at 100°C.

*4. Oxidation*

The 2-oxazolines are fairly stable toward oxidizing agents, as is illustrated by reactions of an oxidation type carried out with variously substituted 2-oxazolines. The ring is stable in these reactions toward nitrating mixtures or alkaline permanganate. Adams and Leffler (53) found it possible to nitrate 2-phenyl-2-oxazolines without cleaving the oxazoline ring. The ordinary nitric acid–sulfuric acid mixture was employed at a temperature not above 10°C. The effect of higher temperatures was not indicated. Billman and Parker (10) successfully oxidized 2-oxazolines containing a 4-methylol group to oxazolinecarboxylic acid according to the equation:




When R was ethyl or methyl, the oxazoline acid was isolated only with difficulty; isolation was easy when R was COOH.

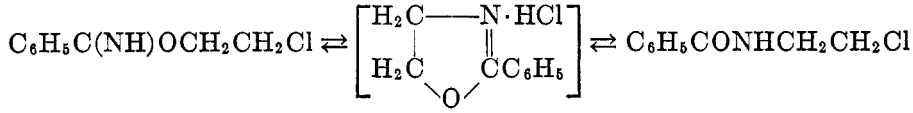
It is surprising to find no mention of conversion of a 2-oxazoline to an oxazole. By analogy with other "aromatic" compounds an instability of the dihydro compound with reference to the unsaturated compound is to be predicted. The failure to observe this transformation indicates a lower order of aromaticity in the oxazoles than other evidence indicates (89).

*5. The iminoester–oxazoline–amide equilibrium*

It has been previously noted that in their studies of the synthesis of oxazolines from iminoesters of β-chloroalcohols, Gabriel and Neumann had observed that the iminoester could be made to yield either the oxazoline or a β-chloroalkylamide. These authors regarded the transformation,

$$C_6H_5C(NH)OCH_2CH_2Cl \xrightarrow{\text{heat}} C_6H_5CONHCH_2CH_2Cl$$

as a simple rearrangement, but Wislicenus and Körber (90) present data indicating that an equilibrium exists, with the oxazoline as an intermediate:




Wislicenus was led to this theory by a reaction of iminoesters previously studied by Wheeler and Johnson (87), which was essentially the same:

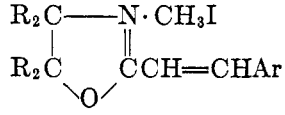
$$C_6H_5C(NH)OC_2H_5 + C_2H_5I \longrightarrow C_6H_5C(OC_2H_5)(NH\cdot C_2H_5I) \xrightarrow{100°C.} C_6H_5CONHCH_2CH_3 + C_2H_5I$$

Wislicenus regards Gabriel's reaction as a Wheeler type in which the use of the alkyl halide is rendered unnecessary by the presence of a $CH_2CH_2Cl$ group in the molecule. The oxazoline corresponds to the intermediate in Wheeler's

reaction. The validity of Wislicenus' mechanism is supported by several facts: (*1*) When an ether solution of the iminoester is concentrated, the residue contains the free oxazoline and the hydrochloride of the iminoester. The iminoester is more basic than the oxazoline and takes up the molecule of hydrogen chloride evolved during the reaction. (*2*) A possible equilibrium is indicated by the fact that when the iminoester hydrochloride and the free oxazoline are heated together, all of the ester does not go to the amide. (*3*) The oxazoline hydrochloride can be converted to the amide in 90 per cent yield by strong heat. The net result in the rearrangement of the iminoester to the amide is the migration of a haloalkyl group from oxygen to nitrogen; the similarity to the migration of an acyl group from oxygen to nitrogen discussed in connection with the hydrolysis of 2-oxazolines should be noted. It should also be pointed out that no attempt to convert an oxazoline hydrochloride back to the iminoester has yet been recorded.

### *6. Activity of a 2-methyl group*

Since 2-methyl-2-oxazoline contains the grouping —$C(CH_3)$=N—, activation of the hydrogen atoms might be expected from analogy with $\alpha$-picoline. Hamer and Rathbone (41) have found that the methiodide and ethiodide of oxazolines undergo typical condensations with aromatic aldehydes. Condensation occurs at the methyl group to yield compounds such as XXIX.



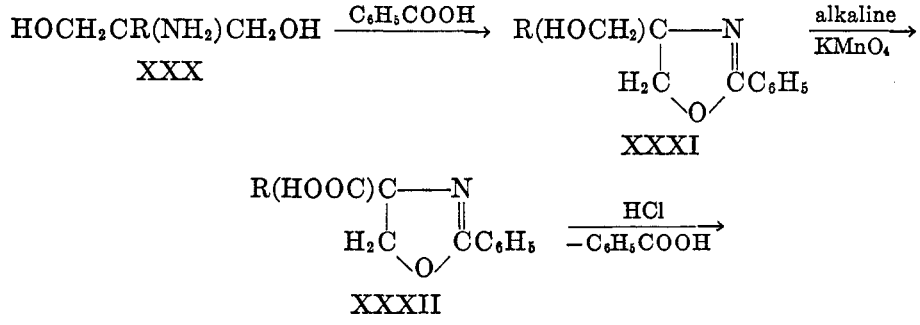
XXIX

Condensations of this type have not been studied by other investigators or with compounds other than the alkiodides of 2-methyl-2-oxazolines. Whether or not the quaternary salts lend an enhanced activity to the side-chain hydrogens is not known.

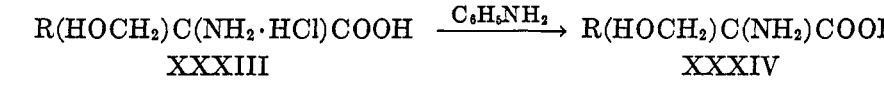
### *7. Synthetic applications*

Oxazolines have been used as starting materials or intermediates in some interesting syntheses. Billman and Parker (10) have developed a process in which oxazolines are intermediates in the synthesis of $\alpha$-amino-$\beta$-hydroxy acids. In searching for a synthetic route to serine, these investigators took advantage of the stability of the oxazoline ring toward mild oxidizing agents, and were thus able to oxidize one hydroxymethyl group in the oxazoline (XXXI) to a carboxyl group.

When R is $CH_3$, XXXI is formed in 67–69 per cent yield and XXXIV in 64.5 per cent yield from XXXI. Attempts to prepare serine by decarboxylation of the oxazoline (XXXI) or the amino acid (XXXIV) when R is COOH were unsuccessful.

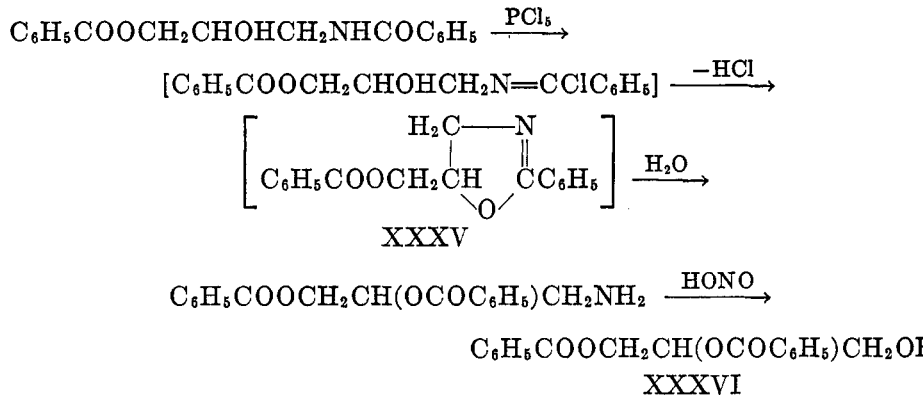


XXX XXXI XXXII



XXXIII XXXIV

It is possible that 2-oxazolines are formed as intermediates in a method proposed by Bergmann, Brand, and Dreyer (5) for preparation of diglycerides (XXXVI) whose acyl groups are in the 1- and 2-positions. The reactions are summarized as follows:



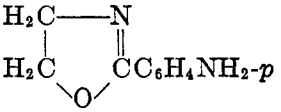
XXXV XXXVI

The oxazoline XXXV was not isolated, but since the net result of the reaction is an acyl migration from nitrogen to oxygen, it may be assumed as an intermediate. This work has been extended by Bergmann (3).

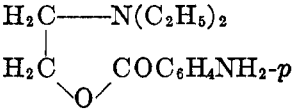
### D. COMMERCIAL AND INDUSTRIAL USES OF 2-OXAZOLINES

Several 2-oxazolines have been considered for use as therapeutic agents. Because of their structural relationship to procaine (XXXVIII), 2-(aminophenyl)-2-oxazolines (XXXVII) might be expected to have some action as local anesthetics. Adams and Leffler, who prepared a series of these compounds (1, 53) and studied their action, found that they did induce local anesthesia. 2-(*m*-Aminophenyl)-2-oxazoline has about the same efficiency as procaine and is only about one-third as toxic. The utility of these compounds as anesthetics is limited by their low water solubility, which at the best is of the order of 1 per cent.

Quaternary salts of XXXVII, which might have increased water solubility, were not reported.

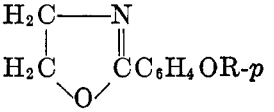


XXXVII

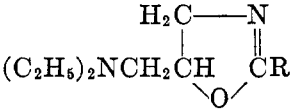


XXXVIII

In addition to the work of Adams and Leffler, Engelmann (26) has found oxazolines containing a *p*-alkoxyphenyl group in the 2-positions (XXXIX) to have action as local anesthetics, and Bockemühl and Knoll (14) have patented compounds such as XL as having therapeutic properties.



XXXIX



XL

R = $C_{17}H_{35}$, $C_{15}H_{31}$

A number of patents describe the use of oxazolines as wetting, emulsifying, or dispersing agents. Compounds used for these purposes always have a long aliphatic group in the 2-position, and are used in the form of salts (47); it has been found that salts of organic acids usually retain their surface activity longer than salts of inorganic acids. Wampner (84) has investigated compounds having hydroxymethyl groups in the 4-position. Compounds of this type have been used as cation-active finishing agents (63).

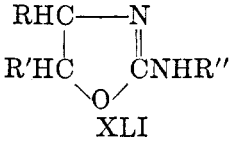
Lactic acid salts of oxazolines with long-chain groups in the 2-position have been used in cosmetic preparations (83). Photographic sensitizers of the cyanine type (41) and methine dyes (43) have been prepared with oxazoline nuclei. Ester amides, prepared from 4-mono- and 4,4-di-substituted-2-oxazolines and acid anhydrides by Tryon (78a), are stated to be useful as solvents or plasticizers and in the preparation of surface-active agents.

## III. Substituted 2-Oxazolines

Of the many conceivable substituted 2-oxazolines, only a few are at all well known. These are the 2-amino, 2-mercapto, and a few hydroxy types. Some which have been listed in the tables in the previous section other than hydrocarbon substitution types are those containing carbethoxy, hydroxymethyl, carbethoxymethyl, and diethylaminomethyl groups. 2-Oxazolines containing vinyl, nitro, halo, aldehydo, or acetyl groups on the ring are apparently unknown. It was noted in Section I that substituted oxazolines, in which the substituent carries a hydrogen and is on a doubly bound ring carbon, may be in tautomeric equilibrium with oxazoles or oxazolidines. This is true of the 2-amino-, 2-mercapto-, and 2-hydroxy-2-oxazolines (X, XI, XII), which are the most widely studied of the 2-oxazolines. Similarities between the syntheses of these substituted types and unsubstituted 2-oxazolines were noted in Section IIA.

### A. PSEUDOUREAS (2-AMINO-2-OXAZOLINES)

The pseudoureas, or 2-amino-2-oxazolines (XLI), are the most widely studied

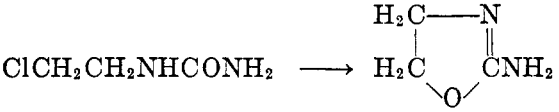


XLI

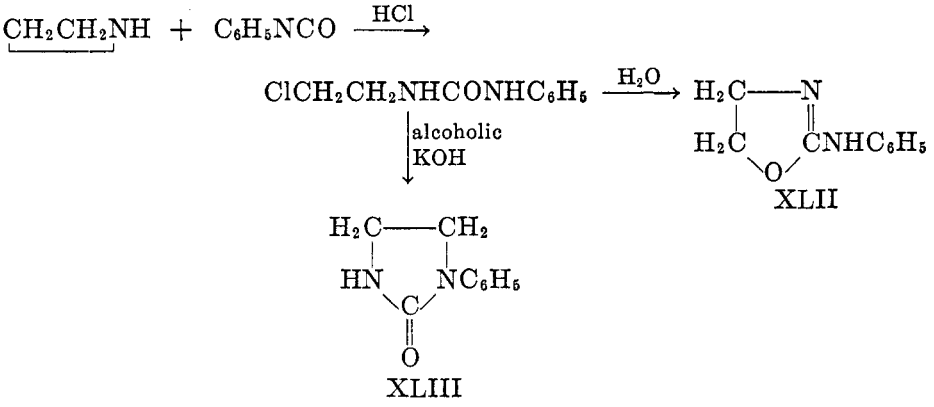
of the substituted 2-oxazolines. Equilibrium with the 2-iminoöxazolidine is possible, and the chemical properties indicate many reactions in both forms. The term "pseudourea" arises from the fact that these compounds are isomers of alkenylureas; thus 2-amino-2-oxazoline is isomeric with *N*-vinylurea and hence is "ethylene pseudourea"; 2-amino-5-methyl-2-oxazoline is isomeric with allylurea and is known as "propylene pseudourea". The compounds are solids and strong bases, forming well-characterized salts (58). 2-Phenylamino-2-oxazolines have been suggested for use as local anesthetics (64), but other possible applications have not developed from rather extensive theoretical studies.

#### *1. Syntheses of pseudoureas*

(*a*) *From β-haloalkylureas:* The hydrochloride of a pseudourea is obtained upon heating the haloalkylurea with water; the addition of alkali releases the free base.



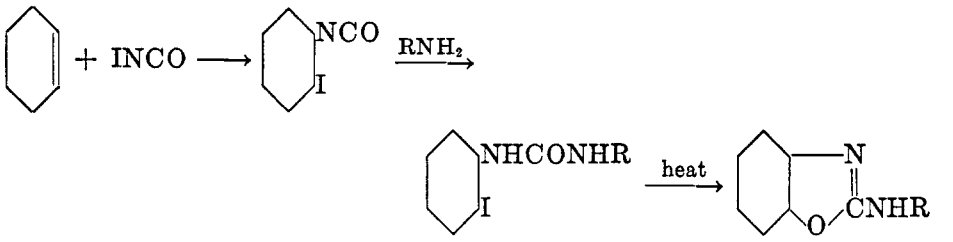
The yields vary from moderate to quantitative. The necessary unsymmetrically substituted ureas are available via several routes. One is the method of Takeda (75), who prepared pseudoureas by heating styrene dibromide, or substituted styrene dibromides, with urea. Gabriel (38) prepared unsaturated ureas from unsaturated amines and isocyanates; the addition of a halogen acid to the double bond then gave the requisite β-haloalkylurea. The product was cyclized to the pseudourea (XLII) on heating with water and to the imidazolidone (XLIII) with alcoholic potassium hydroxide.



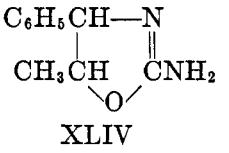
XLII

XLIII

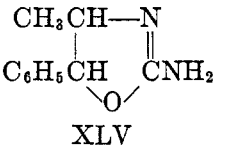
The haloalkylureas can be prepared by the addition of iodine isocyanate to an olefin to form a β-iodoisocyanate, which, when allowed to react with ammonia or an amine, yields the substituted urea. This method was studied by Birckenbach and Linhard (11, 12) in the synthesis of a series of cyclohexane derivatives.




These investigators also used olefins other than cyclohexene; however, the mode of addition of iodine isocyanate to unsymmetrical olefins is not known, and the position of groups in the pseudourea is then difficult to ascertain. Thus, they were able to convert *s*-phenylmethylethylene to the pseudourea in 94 per cent yield, but whether it had the structure XLIV or XLV was not determined; the compound was partially resolved, the *d*-form being isolated.




XLIV




XLV

Another route to the β-haloalkylureas is that originally used by Gabriel (32), in which a β-haloamine is allowed to react with cyanic acid. In this instance, the pseudourea may be obtained directly, without isolation of the intermediate β-halourea.

4-Keto derivatives of pseudoureas are formed by cyclization of α-haloacyl ureas, RCHBrCONHCONHR′, on treatment with alkali. Examples of such reactions have been reported by Aspelund (2a). He has also reported the conversion of 1,5-diphenyl-5-bromobarbituric acid to a pseudourea in a reaction which apparently involves formation of an α-haloacylurea as intermediate. Erlenmeyer and Kleiber (26a) report the formation of 5,5-diethyl-2-imino-4-oxazolidone from guanidine and ethyl α-hydroxy-α-ethylbutyrate.

(*b*) *From β-hydroxyalkylureas and thioureas:* The preparation of a pseudourea from a β-hydroxyalkylurea or thiourea requires a loss of water or hydrogen sulfide in the cyclization and is otherwise similar to the preparation from β-haloalkylureas. In using this method Söderbaum (72) cyclized a β-hydroxyalkylurea by heating with hydrochloric acid or by heating the thio analog with alcoholic mercuric oxide. The compounds prepared were derived from *s*-diphenylethanolamine through conversion to the urea or thiourea with isocyanates or isothiocyanates. The reaction was carried out where R, in XLVa, was H, $CH_3$, $C_2H_5$, $C_6H_5$, and *o*-$CH_3C_6H_4$.

TABLE 4

*Pseudoureas: 2-amino-2-oxazolines*

| SUBSTITUENTS IN 2-AMINO-2-OXAZOLINE* | | | METHOD OF PREPARATION† | YIELD | REFERENCE |
|---|---|---|---|---|---|
| R | R′ | R″ | | | |
| | | | | *per cent* | |
| | | | A;C | 57 | (11, 12, 32, 28) |
| | $CH_3$ | | C | | (29) |
| | $HOCH_2$ | | A;C | 33 | (65, 28) |
| | $ICH_2$ | | A;C | | (30, 65) |
| | $BrCH_2$ | | A;C | | (30, 65) |
| | $ClCH_2$ | | C | 33 | (28) |
| | $C_6H_5$ | | A | | (75) |
| $C_6H_5(CH_3)$ | $CH_3(C_6H_5)$ | | A | 94 | (12) |
| $p$-$CH_3OC_6H_4$ | $CH_3$ | | A | | (75) |
| Cyclohexano | | | A | Quantitative | (12) |
| | | $C_6H_5$ | A | | (38, 58) |
| | $CH_3$ | $p$-$CH_3C_6H_4$ | A | | (58) |
| | $CH_3$ | $m$-$CH_3C_6H_4$ | A | | (58) |
| | $CH_3$ | 2,6-$(CH_3)_2C_6H_3$ | A | | (58) |
| | $CH_3$ | $o$-$CH_3OC_6H_4$ | A | | (58) |
| | $CH_3$ | $m$-$C_2H_5OC_6H_4$ | A | | (58) |
| | $CH_3$ | $C_6H_5$ | A | | (58) |
| | $CH_3$ | $p$-$CH_3C_6H_4$ | A | | (58) |
| | $BrCH_2$ | $BrCH_2CHBrCH_2$ | A | | (68) |
| | $CH_3$ | $CH_3$, $C_6H_5$‡ | A | | (58) |
| Cyclohexano | | $C_6H_5$ | A | 98 | (12) |
| Cyclohexano | | $C_6H_5NH$ | A | 89 | (12) |
| $C_6H_5$ | $C_6H_5$ | R§ | B | | (72) |

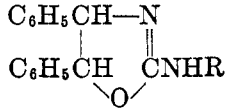
* R, R′, R″ of formula XLI; dash indicates R, R′, or R″ is H.

† A, from β-haloalkylurea; B, from β-hydroxyalkylurea or thiourea; C, from sodium cyanamide.

‡ Second hydrogen on nitrogen replaced by methyl.

§ R is H, $CH_3$, $C_2H_5$, $C_6H_5$, $o$-$CH_3C_6H_4$.

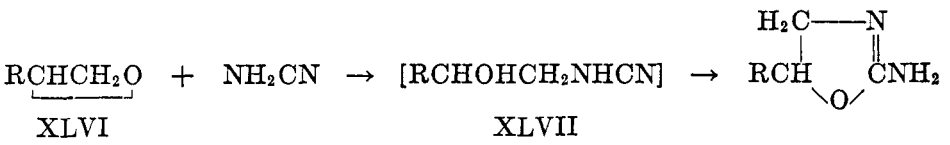
$$C_6H_5CHOHCH(NH_2)C_6H_5 \xrightarrow{RNCS} C_6H_5CHOHCH(C_6H_5)NHCSNHR \quad \text{(XLVa)} \xrightarrow{\text{alcoholic HgO}}$$



The reaction apparently takes a different course when —COOR replaces —CSNHR in XLVa. Thus, ethyl *N*-β-hydroxyethylcarbamate, $HOCH_2CH_2NHCOOC_2H_5$, loses alcohol on heating to form an oxazolidone, not a 2-ethoxy-2-oxazoline (27a).

(*c*) *From sodium cyanamide and chlorohydrins:* Synthesis of pseudoureas (see table 4) from sodium cyanamide and chlorohydrins has no similarity to the syntheses of oxazolines as do the two preceding syntheses. Fromm and coworkers (28, 29, 30, 31) have described the reaction. The mechanism is not

clear, but Fromm proposes that the sodium cyanamide reacts with the water present to form sodium hydroxide, which in turn dehydrohalogenates the chlorohydrin to the epoxide. Reaction of the epoxide (XLVI) with cyanamide then follows to form an unstable intermediate (XLVII), which rearranges to the pseudourea.

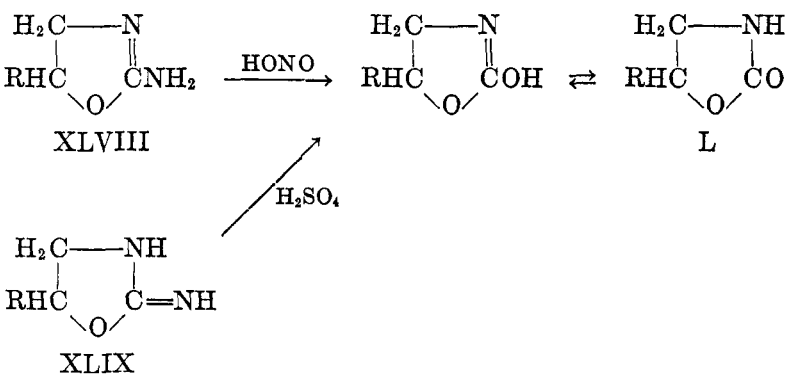



XLVI XLVII

This mechanism is supported by the isolation of the pseudourea from the reaction when an epoxide is substituted for the chlorohydrin. Reaction between the chlorohydrin and sodium cyanamide to give the intermediate XLVII is not excluded by this evidence. The method has been successfully used with ethylene chlorohydrin and glycerol dichlorohydrin. A yield of 33 per cent of 2-amino-5-chloromethyl-2-oxazoline was reported from the epichlorohydrin. Reaction with chloroacetic acid gave an undescribed product.

*2. Reactions of pseudoureas*

The tautomerism of pseudoureas has been extensively investigated, chiefly by Fromm (28, 29, 30), who has established that these compounds react either as 2-amino-2-oxazolines (XLVIII) or 2-iminoöxazolidines (XLIX).

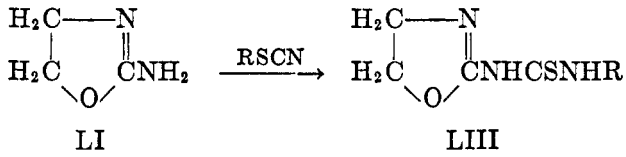



XLVIII L XLIX

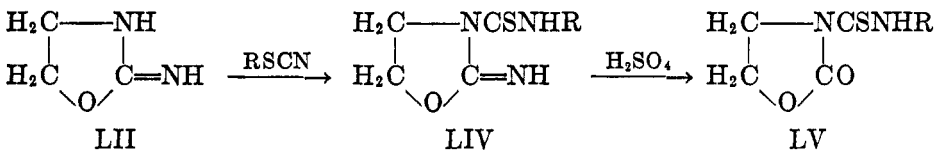
Thus pseudoureas are converted by heating with sulfuric acid to the oxazolidone (L); this can best be explained as hydrolysis of the imide form. This reaction was carried out with R = H, $CH_2Cl$, $CH_3$, and $CH_2SC_7H_7$. On the other hand, nitrous acid also produces the oxazolidone, and probably reacts with the amino form (XLVIII). This latter reaction has been carried out only with R = H, but there is no reason to doubt that it is general.

An independent line of investigation confirmed the existence of these tautomeric forms. Fromm (29, 30) found that isothiocyanates react with pseudoureas to form two thioureas, one high-melting and one low-melting. The low-melting compound (LIV) was assigned the imino structure, since sulfuric acid

converts it to the oxazolidone (LV). The other compound (LIII) was then assumed to be a derivative of the primary amine (LI). The low-melting compound can be irreversibly converted to the high by heating.



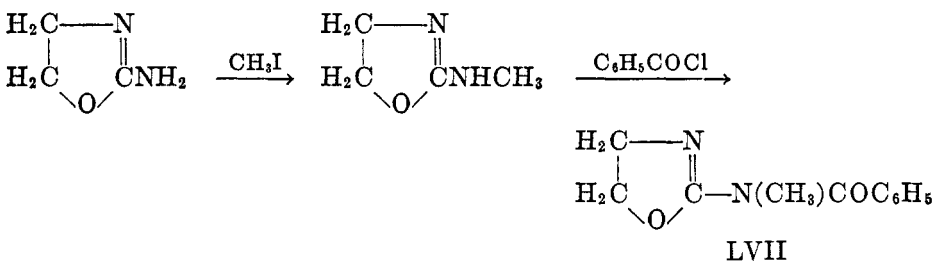
LI LIII



LII LIV LV

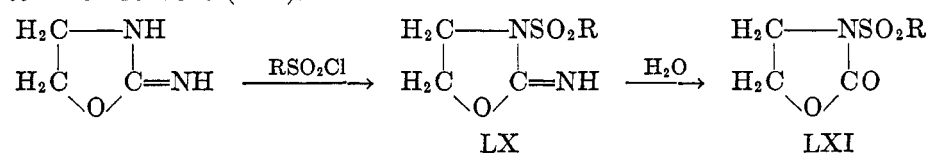
In connection with this study, Fromm (29) noted that 2-amino-4-phenyloxazole formed only one thiourea, indicating that in the oxazole series this tautomerism either does not exist or is very limited.

Other reactions of pseudoureas show that either the imino or the amino form can react (30). An *N*-methylpseudourea is obtained on reaction with methyl iodide. The benzoyl derivative (LVII) of the *N*-methylpseudourea is stable toward dilute acid and is therefore thought to be an *N*,*N*-derivative of the amino form and not a derivative of the imino form.



LVII

Acetylation with acetic anhydride and sodium acetate gives an acetyl derivative of the 2-amino-2-oxazoline form. The 2-alkylamino-2-oxazolines are similarly acetylated. Sulfonyl chlorides apparently attack either the ring nitrogen or both ring and side-chain nitrogen. In either case, the imino form is the one which reacts. Thus, benzenesulfonyl chloride forms the derivative LX, whose constitution was assigned (29) on the basis of the fact that it may be hydrolyzed to an oxazolidone (LXI).

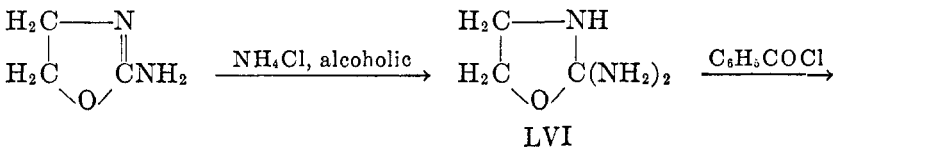


LX LXI

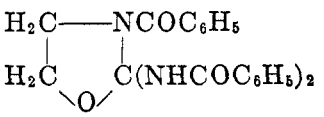
Jensen (48) discovered that when acetylsulfanilyl chloride is used and the reaction carried out in pyridine, both nitrogen atoms are substituted; in acetone,

however, only the 3-acetylsulfanilyl derivative was formed. Birckenbach and Linhard (12) report that hypobromite reacts with a pseudourea in the amino form to give an *N*,*N*-dibromo derivative.

A peculiar reaction with ammonia or amines has been described (28, 29). When a pseudourea is heated with ammonium chloride, or when its hydrochloride is heated with ammonia, addition to the double bond of the amino form occurs and a 2,2-diaminoöxazolidine (LVI) is formed (28, 29). Amines react similarly. The product forms a tribenzoyl derivative (LVII).




LVI




LVII

Rupture of the ring takes place under some conditions. Thus, at 100°C. with alcoholic ammonium chloride a guanidine derivative (LIX) is formed from 2-amino-5-chloromethyl-2-oxazoline (29).

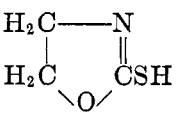
$$HCl \cdot H_2NC(=NH)NHCH_2CHOHCH_2Cl$$

LIX

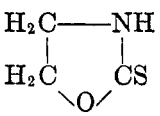
Rundqvist (65) has observed that sodium amalgam converts a 5-bromomethyl-2-amino-2-oxazoline to allylurea.

### B. 2-MERCAPTO-2-OXAZOLINES

As the 2-amino-2-oxazolines, the 2-mercapto derivatives are capable of existing in the tautomeric oxazolidone form and react in either the thiol form (LXII) or the thione form (LXIII).




LXII



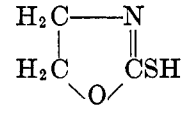

LXIII

2-Mercapto-2-oxazolines are formed by the action of carbon disulfide on β-hydroxyamines. Thus, Bruson and Eastes (20) converted 1-amino-2-hydroxy-2-methylpropane to 5,5-dimethyl-2-mercapto-2-oxazoline in almost quantitative yield. A similar method was employed by Sergeev (69), who found that β-hydroxyethylamine reacted first to form an intermediate (LXIV) which was converted by methyl chlorocarbonate to LXV, which upon long standing or upon heating formed the oxazoline (LXVI).

$$HOCH_2CH_2NH_2 + CS_2 \rightarrow (HOCH_2CH_2NH)_2CS_2H \xrightarrow{ClCOOCH_3}$$

LXIV

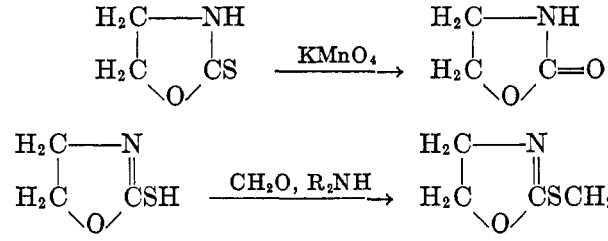
$$HOCH_2CH_2NHCS_2COOCH_3 \rightarrow$$



LXV LXVI

The formation of some 2-mercaptoöxazoline in the reaction between chlorohydrin and potassium thiocyanate has been reported (70).

Reactions of both the thione form (LXII) and the thiol form (LXIII) are known. Permanganate converts the compound, presumably the thione form, to an oxazolidone (69). Iodine reacts, but the disulfide which might be expected was not isolated (60). Formaldehyde and amines replace the sulfhydryl hydrogen with a $—CH_2NR_2$ group (57).



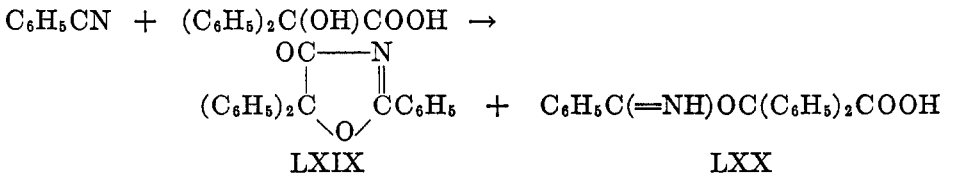
Various 2-mercapto-2-oxazolines have been evaluated for different uses. 2-Mercapto-2-oxazoline has antithyroid activity (60), and 5,5-dialkyl-2-mercapto-2-oxazolines have found some use in sprays and dusting powders for plants (19). A series of compounds were prepared by Mathes (57) through the action of formaldehyde and ammonia or amines on the 2-mercaptoöxazoline and studied as vulcanization accelerators. Of these, bis(5,5-dimethyl-2-oxazolin-2-ylmercaptomethyl)isopropylamine was said to have excellent properties as a vulcanization accelerator for rubber.

### C. 4-KETO-2-OXAZOLINES

The 4-keto-2-oxazolines (LXVII) are tautomeric with 4-hydroxyoxazoles (LXVIII).

LXVII LXVIII

The 4-ketopseudoureas (2a) are mentioned above. One other 4-keto-2-oxazoline has been described. The 2,5,5-triphenyl derivative (LXIX) was prepared by Japp and Findlay (45, 46) from benzonitrile and benzilic acid.

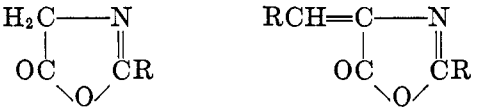


LXIX LXX

Benzimidoxydiphenylacetic acid (LXX) was also isolated from the reaction mixture and converted to the oxazoline by heating with acetic anhydride. The oxazolone is decomposed by heating with alkali or concentrated sulfuric acid. Ring closure of haloimides of the type $BrCH_2CONHCOR$ provides a source of 4-keto-2-oxazolines.

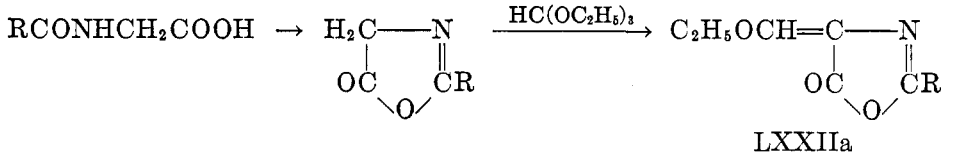
### D. 5-KETO-2-OXAZOLINES

The 5-keto-2-oxazolines (LXXI) are the familiar azlactones. These are the $\alpha$-acylamino acid inner anhydrides. Both the unsubstituted and 4-arylene types



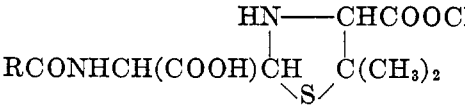
LXXI LXXII

(LXXII) have been reviewed elsewhere (21) and need not be discussed here. Recent work (81a) on the synthesis of penicillin has started with various 4-hydroxymethylene-5-keto-2-oxazolines (LXXIIa) and their derivatives. The preparation of such derivatives from benzoyl- and some acyl-glycines, acetic anhydride, and ethyl orthoformate has been reported (2b). Others have been studied (24a, 81a). Those reported in the literature are listed in table 5. This preparation may take place through condensation of the active methylene group of the azlactone with ethyl orthoformate.



LXXIIa

The hydroxymethylene compound itself is the enol form of the aldehyde. The objective of many attempts to synthesize penicillin (24a) has been to condense this aldehyde or one of its derivatives with penicillamine ($\beta,\beta$-dimethylcysteine). The hypothesis that the synthesis would proceed through thioacetal formation followed by ring closure to the thiazolidine is supported by known similar reactions. Thus, acetone reacts with cysteine to form 2,2-dimethyl-4-carboxythiazolidine (61a). The many unsuccessful attempts to achieve this synthesis and the extremely low yields finally obtained suggest the improbability of the reaction taking this course and of the oxazolone structure for penicillin. The unsuccessful anhydrization of the penicilloates is similar evidence indicating the



improbability of the oxazolone form (24a). A derivative of penicillin which has an oxazolone ring is formed on reaction of the methyl ester of penicillin with

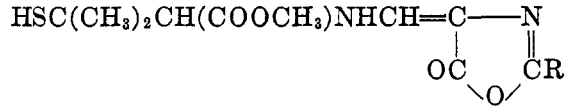
TABLE 5

*4-Substituted-5-keto-2-oxazolines**

| 4-SUBSTITUENT | 2-SUBSTITUENT | REFERENCE |
|---|---|---|
| $(CH_3)_2C=$ | $C_6H_5$ | (2b) |
| $CH_3OCH=$ | $C_5H_{11}$ | (81a) |
| $CH_3OCH=$ | $C_6H_5CH_2$ | (81a) |
| $CH_3OCH=$ | $C_6H_5CH_2$ | (24a, 81a) |
| $C_2H_5OCH=$ | $CH_3$ | (81a) |
| $C_2H_5OCH=$ | $C_5H_{11}$ | (2b) |
| $C_2H_5OCH=$ | $C_6H_5$ | (2b, 24a, 81a) |
| $C_2H_5OCH=$ | $C_6H_5CH=CH$ | (2b) |
| $C_2H_5OCH=$ | $p$-$O_2NC_6H_4CH_2$ | (81a) |
| $C_2H_5OCH=$ | $p$-$O_2NC_6H_4CH=CH$ | (81a) |
| $C_3H_7OCH=$ | $C_6H_5$ | (2b) |
| $HOCH=$ | $C_3H_7$ | (81a) |
| $HOCH=$ | $C_5H_{11}$ | (81a) |
| $HOCH=$ | $C_6H_5$ | (2b) |
| $HOCH=$ | $C_6H_5CH_2$ | (57a) |
| $HOCH=$ | $C_6H_5CH=CH$ | (2b) |
| $CH_3SCH=$ | $C_6H_5$ | (81a) |
| $p$-$CH_3CONHC_6H_4OCH=$ | $C_6H_5$ | (81a) |

**Added in proof:* See also *The Chemistry of Penicillin*, p. 743 ff. Princeton University Press, Princeton, New Jersey (1949).

mercuric chloride (26b, 57a). This product, the methyl ester of penicillenic acid, has been assigned the structure:

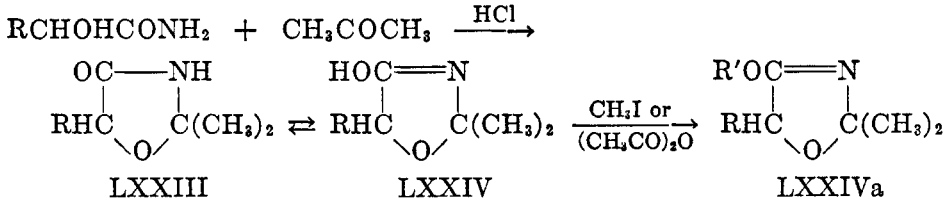


Hydrolysis of this ester with sodium hydroxide gives 4-hydroxymethylene-2-benzyloxazolone (57a).

## IV. 3-Oxazolines

Neither 3-oxazoline itself nor any of its hydrocarbon derivatives are known. A report by H. O. L. Fischer, Dangschat, and Stettiner (27) contains the only known description of compounds with a 3-oxazoline ring.[8] These were obtained as *O*-methyl and *O*-acetyl derivatives (LXXIVa) of 4-oxazolidones (LXXIII). Zeisel alkoxyl determination established the *O*-methyl structure. Enolization to form a 3- instead of a 4-oxazoline ring was based on the similarity to the formation of *O*-alkyl derivatives of amides.

[8] *Note added in proof:* Others are reported in *The Chemistry of Penicillin*, Princeton University Press, 1949, pp. 739–42, as pseudoxazolones.




LXXIII ⇄ LXXIV → LXXIVa

The 4-oxazolidones were prepared from amides of mandelic, glycolic, and lactic acids. This synthesis is similar to the synthesis of oxazolidines from aldehydes or ketones and β-hydroxyamines (58a). The wide applicability of the oxazolidine synthesis suggests that this synthesis of 4-oxazolidones and their derivative 4-hydroxyoxazolines can be extended.

TABLE 6

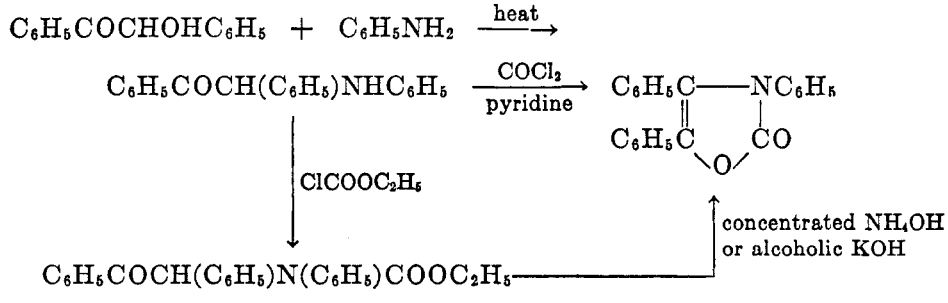
*4-Oxazolines**

| 3-SUBSTITUENT | 4-SUBSTITUENT | 5-SUBSTITUENT | YIELD |
|---|---|---|---|
| | | | *per cent* |
| $C_6H_5$ | $C_6H_5$ | $C_6H_5$ | 80 |
| *o*-$CH_3C_6H_4$ | $C_6H_5$ | $C_6H_5$ | |
| *m*-$CH_3C_6H_4$ | $C_6H_5$ | $C_6H_5$ | |
| *p*-$CH_3C_6H_4$ | $C_6H_5$ | $C_6H_5$ | |
| $C_6H_5$ | H | $C_6H_5$ | Almost quantitative |
| *o*-$CH_3C_6H_4$ | H | $C_6H_5$ | 60 |
| *p*-$CH_3C_6H_4$ | H | $C_6H_5$ | |
| *m*-$CH_3C_6H_4$ | H | $C_6H_5$ | 60 |
| $C_{10}H_7$ | H | $C_6H_5$ | |

* Reported by McCombie and coworkers (55, 56).

## V. 4-Oxazolines

4-Oxazoline is not known and neither are any of its simple hydrocarbon derivatives. The only known types are the 3,5-diaryl and 3,4,5-triaryl-2-keto-4-oxazolines prepared by McCombie and coworkers (55, 56) by the following series of reactions:




*N*-Phenacylaniline, $C_6H_5COCH_2NHC_6H_5$, gave 3,5-diphenyl-2-keto-4-oxazoline. Others are included in table 6.

These compounds are highly stable substances. 3,4,5-Triphenyl-2-keto-4-oxazoline is unchanged by several hours refluxing with aqueous acid, alcohol, or phosphorus pentachloride. As would be expected from the negativity of the *N*-substituent, this substance is not sufficiently basic to yield a hydrochloride or chloroplatinate. Typical ketone reactions are not shown; heating in a sealed tube with phenylhydrazine gives no phenylhydrazone. Reduction with sodium amalgam gives no clear-cut results; the oxazolone is sometimes reduced to bibenzyl and sometimes recovered unchanged. The hydrogen atom of carbon number four, in compounds having no 4-substituent, cannot be replaced by bromine.

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