

THE CHEMISTRY OF THE OXAZOLES

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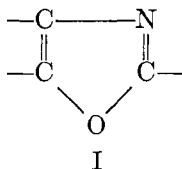
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CONTENTS

I. Introduction.....	401
II. Methods of preparation.....	403
A. From α -acylamino-carbonyl compounds.....	403
B. From acyl derivatives of α -amino acid esters.....	406
C. From α -amino acids.....	407
D. From benzalaminoacetals.....	409
E. From desyl esters and ammonia.....	410
F. From aromatic aldehydes and aromatic aldehyde cyanohydrins.....	410
G. From amides and α -haloketones and α -haloaldehydes.....	413
H. From benzil.....	415
I. By reduction of oxidooxazoles.....	419
J. From benzoin and nitriles.....	420
III. Properties.....	421
A. Physical properties.....	421
B. Chemical properties.....	423
1. Basicity.....	424
2. Salt formation.....	425
3. Stability to acids and bases.....	426
4. Oxidation.....	429
5. Nitration of phenyloxazoles.....	429
6. Reduction.....	430
7. Unclassified reactions.....	432
8. Pharmacology.....	432
C. Properties of substituted oxazoles.....	433
1. Aminooxazoles.....	433
2. Aminophenyloxazoles.....	433
3. Ethoxyoxazoles.....	434
4. Chlorooxazoles.....	436
5. Oxidooxazoles.....	436
IV. Structure.....	438
V. References.....	440

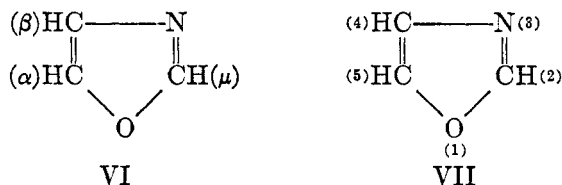
I. INTRODUCTION

The oxazoles, which are compounds containing the nucleus shown below (I),



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unknown constitution had been obtained from the reaction of acetamide and other amides with phenacyl bromide by Blümlein (13) and later by Lewy (75, 76, 77). Hantzsch recognized the similarity between this synthesis and the analogous thiazole synthesis and suggested that the products were oxazoles. The name "oxazole" was proposed by Hantzsch, along with a lettering system to indicate the positions of substituents (43, 44). This system of lettering, which is used only in the older literature, and the present system of numbering positions are illustrated in formulas VI and VII, respectively.

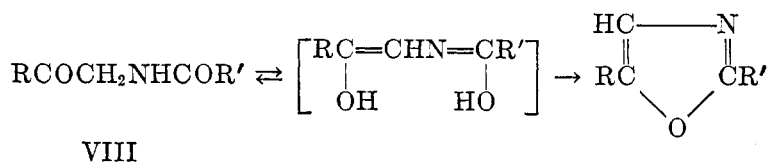


II. METHODS OF PREPARATION

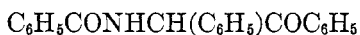
The mechanisms of the reactions used in the syntheses of the oxazoles are not sufficiently well understood to form a basis for a systematic classification of the syntheses. Some of the methods are similar to ring-forming reactions observed in the preparation of furans and pyrroles. The dehydration of open-chain compounds of the formula $RCONHCH_2CO-$ to oxazoles recalls the preparation of 2,5-dimethylfuran from acetylacetone, while the preparation of oxazoles from desyl esters and ammonia is similar to the preparation of 2,5-dimethylpyrrole from acetylacetone and ammonia (12). The mechanisms of these reactions are straightforward. Mild conditions are used and the reactions are generally considered to take place without rearrangements. They will be discussed first for this reason. The methods which will be discussed subsequently proceed by mechanisms which are not so clearly defined. In some or even all of these reactions intermediates may be formed which are cyclized by one of the above methods, i.e., either dehydration or reaction with ammonia. Usually, however, the information necessary to make a final decision as to the course of the reaction is not available and it is, therefore, more convenient to classify the preparative methods in terms of starting materials, as has been done in the following discussion.

A. FROM α -ACYLAMINOCARBONYL COMPOUNDS

The dehydration of acylaminocarbonyl compounds (VIII) to oxazoles is similar to the preparation of other five-membered oxygen- and sulfur-containing rings from 1,4-dicarbonyl compounds (62a, 118a). The general reaction can be written as follows:



The first description of this reaction was made by Robinson (96) in 1909. Shortly thereafter Gabriel (35) reported an independent investigation in which he also described this synthesis of oxazoles. In 1845, however, Laurent—and since then many others (20, 81)—had converted benzilimide, a compound of then unknown structure, to azobenzil, also of unknown structure, by a dehydration with sulfuric acid. The recent work of Davidson, Weiss, and Jelling (20) has shown that benzilimide is *N*-desylbenzamide (IX), and azobenzil had pre-

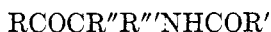


IX

viously been identified as 2,4,5-triphenyloxazole (V) by Japp (54, 55). The present synthesis has been the subject of oxazole research for over a hundred years and is one of the classic reactions of oxazole chemistry.

Two experimental procedures have been used in the greater number of examinations of this reaction. Gabriel (35, 36) and others (7, 99) heat equimolar parts of the amide and phosphorus pentachloride on the steam bath. The use of excess chloride produces halogen-containing compounds (discussed under chloro-oxazoles). Better yields are obtained by the method of Robinson (78, 81, 95, 96). The amide is dissolved in concentrated sulfuric acid and, after the solution has stood at room temperature for a few minutes to half an hour, water is added to precipitate the oxazole as the free base. Formation of the oxazole can often be detected by the appearance of fluorescence in the sulfuric acid solution. In some cases, as with 2-phenyl-5- α -naphthyloxazole, the reaction is so rapid and complete as to indicate that the acylamino compound cannot exist in sulfuric acid.

A variety of examples, summarized in table 1, are available to indicate the scope of this reaction. In the general formula for the acylaminocarbonyl compound (X) variations in all of the groups R, R', R'', and R''' have been studied.



X

Since no oxazole has been obtained from α -benzoylaminoisobutyrophenone where both of the groups R'' and R''' are methyl (7), it appears that one of these two must be hydrogen if an oxazole is to be formed. If R'' is hydrogen, oxazoles can then be obtained when R''' is hydrogen, an aliphatic group, or an aromatic group (7, 20, 78, 81). Variations in the acyl radical have shown that oxazoles can be prepared when the R' group is hydrogen, an aliphatic group, or an aromatic group. Most of the syntheses have been conducted with aromatic substituents for both R and R'. Only three examples where one of these is aliphatic and only one where both are aliphatic have been described. There is no report of the successful conversion of an aldehyde, where R is hydrogen, to an oxazole. Robinson (96) reported an intention to synthesize oxazole from formylaminoacetaldehyde, $\text{OHCCH}_2\text{NHCHO}$, by this reaction,

but no further report on the results of this experiment has been found. Aldehydes can be converted to oxazoles through a variation of the present reaction

TABLE 1
Oxazoles from acylaminocarbonyl compounds (X)

R*	R''	DEHYDRATING AGENT	YIELD	REFERENCE
H	H		†	(96)
H	<i>o</i> -O ₂ NC ₆ H ₄	H ₂ SO ₄ -P ₂ O ₅	No oxazole	(16)
CH ₃	CH ₃	PCl ₅		(36)
CH ₃	C ₆ H ₅	PCl ₅		(36)
C ₆ H ₅	H	PCl ₅		(7)
C ₆ H ₅	CH ₃	PCl ₅		(36)
C ₆ H ₅	C ₆ H ₅	PCl ₅		(35)
C ₆ H ₅	C ₆ H ₅	H ₂ SO ₄		(96)
C ₆ H ₅	<i>o</i> -CH ₃ C ₆ H ₄	H ₂ SO ₄	Almost theoretical	(78)
C ₆ H ₅	<i>m</i> -CH ₃ C ₆ H ₄	H ₂ SO ₄	Almost theoretical	(78)
C ₆ H ₅	<i>p</i> -CH ₃ C ₆ H ₄	H ₂ SO ₄	Almost theoretical	(78)
C ₆ H ₅	<i>p</i> -CH ₃ OC ₆ H ₄	H ₂ SO ₄		(78)
C ₆ H ₅	<i>o</i> -ClC ₆ H ₄	H ₂ SO ₄		(78)
C ₆ H ₅	C ₆ H ₅ CH=CH	H ₂ SO ₄		(78)
C ₆ H ₅	<i>o</i> -O ₂ NC ₆ H ₄	H ₂ SO ₄		(78)
C ₆ H ₅	<i>m</i> -O ₂ NC ₆ H ₄	H ₂ SO ₄		(78)
C ₆ H ₅	<i>p</i> -O ₂ NC ₆ H ₄	H ₂ SO ₄		(78)
C ₆ H ₅	α-C ₁₀ H ₇	H ₂ SO ₄	Theoretical	(78)
C ₆ H ₅	α-C ₁₀ H ₇	POCl ₃ , SOCl ₂	Less than with H ₂ SO ₄	(78)
C ₆ H ₅	C ₆ H ₅ CH ₂	H ₂ SO ₄		(96)
<i>p</i> -CH ₃ OC ₆ H ₄	C ₆ H ₅	H ₂ SO ₄		(78)
<i>p</i> -CH ₃ OC ₆ H ₄	C ₆ H ₅ CH=CH	H ₂ SO ₄		(78)
α-C ₁₀ H ₇	C ₆ H ₅	H ₂ SO ₄		(78)
C ₆ H ₅ CH ₂	C ₆ H ₅	H ₂ SO ₄		(96)
3,4-(CH ₃ O) ₂ C ₆ H ₃	C ₆ H ₅	H ₂ SO ₄		(96)
3,4-(CH ₃ O) ₂ C ₆ H ₃	C ₆ H ₅ CH ₂	H ₂ SO ₄		(96)
3,4-(CH ₃ O) ₂ C ₆ H ₃	3,4-(CH ₃ O) ₂ C ₆ H ₃	H ₂ SO ₄	†	(124)
<i>p</i> -CH ₃ C ₆ H ₄	C ₆ H ₅	PCl ₅	18 per cent	(99)
C ₆ H ₅ CH=CH	C ₆ H ₅	H ₂ SO ₄	Excellent	(31)
<i>p</i> -CH ₃ C ₆ H ₄	CH ₃	PCl ₅		(99)
C ₆ H ₅	CH ₃	H ₂ SO ₄	‡	(7)
C ₆ H ₅	C ₆ H ₅	H ₂ SO ₄	‡	(78)
C ₆ H ₅	C ₆ H ₅	H ₂ SO ₄	87 per cent §	(20, 81)
C ₆ H ₅	C ₆ H ₅	PCl ₅	¶	(7)

* R and R' of formula X.

† Discussion but no experimental data.

‡ R'' of formula X is CH₃; R''' is H and an oxazole is formed.

§ R'' of formula X is C₆H₅; R''' is H and an oxazole is formed.

¶ R'' and R' of formula X are CH₃ and no oxazole is formed.

(16, 98) in which an acyl derivative of aminoacetal is cyclized by treatment with sulfuric acid and phosphoric anhydride. *p*-Nitrobenzoylaminoacetal (XI)

can be converted to 2-*p*-nitrophenyloxazole in 46 per cent yield, while the corresponding *o*-nitro derivative gives a 6 per cent yield of the oxazole.



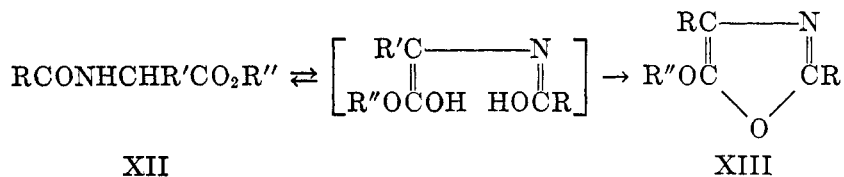
XI

This modified process has not been successful when the free aldehyde is used (16) or when sulfuric acid or phosphoric anhydride is used alone (7, 16).

There has been very little speculation about the mechanism of this synthesis. The conditions under which this reaction occurs are comparatively mild, and for this reason it has been assumed that the dehydration takes place through the enol form without rearrangement to give the 2,5-disubstituted derivative, as indicated in the above equation. It is consistent with this hypothesis that α -benzoylaminoisobutyrophenone gives no oxazole. The oxazoles prepared by this method have been used as standards for comparison with the oxazoles prepared by other methods to establish the position of the substituents in the oxazoles formed in such other reactions. These comparisons will be discussed in connection with preparations F and G in the following discussion.

B. FROM ACYL DERIVATIVES OF α -AMINO ACID ESTERS

The synthesis of oxazoles from acyl derivatives of α -amino acid esters (XII) is similar to the cyclization of α -acylamino carbonyl compounds (VIII). The product, a 2,4-disubstituted 5-alkoxyoxazole (XIII), is probably formed by dehydration of the enolized ester.



XII

XIII

Karrer and his collaborators, who first described this reaction (63, 64), have prepared a number of oxazoles from a variety of acyl derivatives of amino acid esters in their study, to be discussed subsequently, of the possible occurrence of such compounds as a unit in the polypeptide chain. Earlier studies by Rügheimer (101) on the reaction of dehydrating reagents on the ethyl ester of hippuric acid had led to the formation of products which have never been completely characterized. Weiss in 1893 (116, 117) had obtained compounds, for which he proposed no structure, from the phenyl ester of hippuric acid on treatment with phosphorus oxychloride. On the basis of the properties described, Karrer and Gränacher (63) have stated that Weiss's compound was certainly an oxazole. The reaction is carried out by warming a chloroform solution of the ester with phosphorus pentachloride or phosphorus pentoxide on the water bath for 5 min. The product is isolated by ether extraction of the aqueous alkali-treated reaction mixture. A yield of 40 per cent of 2-phenyl-5-ethoxyoxazole is obtained from ethyl benzoylglycinate. A list of the oxazoles prepared

by this method is given in table 2 along with some reported unsuccessful attempts to apply this reaction.

C. FROM α -AMINO ACIDS

It is perhaps to be anticipated that oxazoles can be obtained from α -amino acids when it is known that α -amino ketones and α -amino acid esters can be converted to oxazoles. The synthesis from the ketones and esters proceeds through dehydration of their acylamino derivatives, and it is therefore to be expected that such a process could be used in the preparation of oxazoles from amino acids. It was, in fact, in demonstrating that the heterocyclic compounds

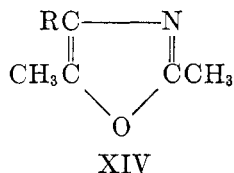
TABLE 2
Oxazoles from acyl derivatives of α -amino acid esters

R' OF FORMULA XII	R OF FORMULA XII	R' OF FORMULA XII	REFERENCE
Ethyl	Methyl	Hydrogen	(41, 63)
	Methyl	Methyl	(64)
	Methyl	Isopropyl	(64)
	Methyl	Isobutyl	(40, 63)
	Propyl	Isobutyl	(64)
	Isobutyl	Hydrogen	(64)
	<i>sec</i> -Butyl	Isobutyl	(64)
	<i>n</i> -Pentadecyl	Hydrogen	(64, 87)
	Phenyl	Hydrogen	(40, 63, 64)
	Campholyl	Isobutyl	(64)
Phenyl	Phenyl	Hydrogen	(116)
	Phenyl	Phenyl	(116)
Ethyl*	<i>n</i> -Amyl	Hydrogen	(64)
	<i>n</i> -Heptyl	Hydrogen	(64)
	<i>n</i> -Undecyl	Hydrogen	(64)
	Chloromethyl	Isobutyl	(40)
	Phthalylglycyl	Isobutyl	(40)
	1,2-Diphenylethyl	Isobutyl	(40)

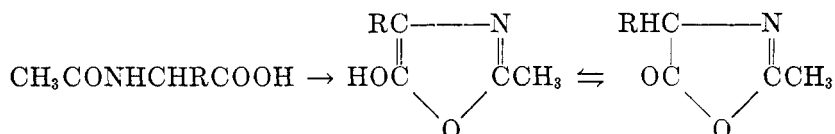
* No oxazole is formed.

obtained by the treatment of proteins with acetic acid and acetyl chloride were oxazoles that Wrede and his collaborators (120, 121, 122, 123) were led to the discovery that α -amino acids can be converted to oxazoles by a similar treatment. The preferred procedure for conducting the synthesis combines two steps to give about a 15 per cent yield of the oxazole (122). The first step is an acetylation type reaction in which a mixture of the amino acid, acetic anhydride, and sodium acetate is heated to boiling for 15 min. In the second step the mixture is dehydrated and decarboxylated by treatment with phosphorus pentachloride at 100°C. for 15 min. The α -amino acids which have been successfully converted to oxazoles are glycine, alanine, valine, leucine, phenylalanine, tyrosine, and glutamic acid, while those which have been tried and found not to give oxazoles

are asparagine, tryptophan, and formylglycine. In all cases 2,5-dimethyloxazoles with varying substituents in the 4-position (XIV) are formed.

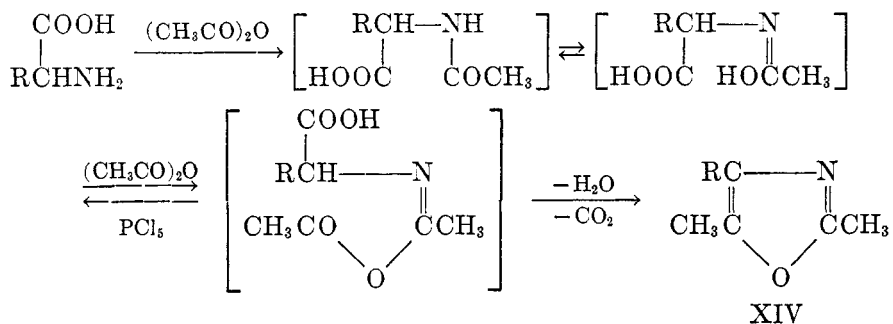


The formation of a 2,5-dimethyloxazole with each amino acid requires an explanation. A simple dehydration of the acylamino acid, such as takes place with the amino acid esters described in the previous method, would lead to the formation of 2-methyl-5-hydroxyoxazoles or their oxazolone tautomers.



That the reaction may take this course, at least in the acetylation step, is substantiated by the reports of Carter and his collaborators (14, 15), who have observed that azlactones are formed from acylamino acids and acetylating reagents. Such a reaction does not lead to the formation of a 2,5-dimethyloxazole and cannot explain the course of the present reaction. It may, however, be a side reaction which contributes to the low yields.

Wrede and his collaborators explain the reaction by the following sequence of steps:

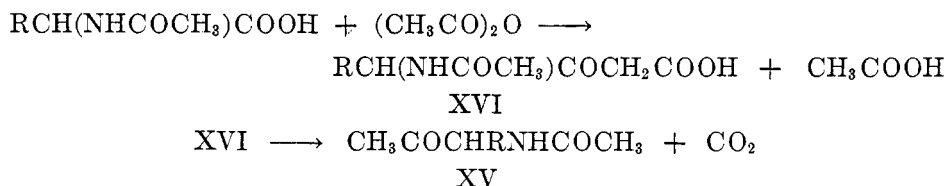


This proposal formulates the conversion of an α -amino acid to a 2,5-dimethyloxazole derivative but needs supporting experimental data before it can be accepted as a statement of the mechanism of the reaction.

The following proposed mechanism for this synthesis is based on the available information on the acetylation of α -amino acids and on the cyclization of α -acylamino ketones to oxazoles. It is proposed that an acylamino ketone (XV) is formed in the acetylation step and that this is dehydrated in the second step



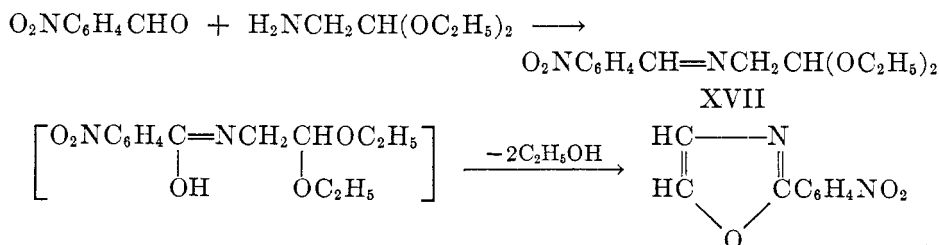
to a 2,5-dimethyloxazole. That such a compound as XV is formed in the acetylation of α -amino acids has been established by Levene and Steiger (73, 74) and by Dakin and West (18, 19). They have shown that the acetylation of amino acids proceeds with the evolution of carbon dioxide and the introduction of two acetyl groups, one on the nitrogen and one on the α -carbon atom. The acetylation is carried out by heating the amino acid with acetic anhydride in the presence of pyridine under conditions similar to those of the first step in the process for the preparation of the oxazoles. It has been proposed that this reaction proceeds by the condensation of the acetylamino acid first formed with more acetic anhydride to a β -keto acid (XVI), which decarboxylates to the ketone (XV).



The dehydration of acylamino ketones to oxazoles has been described previously, and the conditions for this reaction are those which are used in the second step in the present oxazole synthesis. The yields in the two separate steps with some examples are reported to be almost theoretical. The yields reported for the total synthesis are so much poorer as to indicate that proper selection of the reaction conditions will lead to the formation of oxazoles in higher yields.

D. FROM BENZALAMINOACETALS

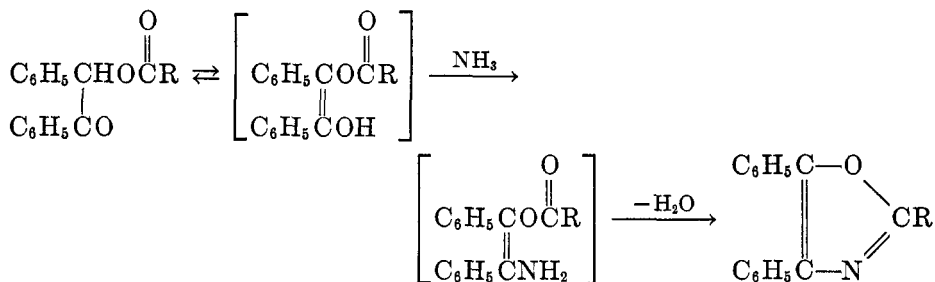
A method of preparation of oxazoles which is related to the syntheses from acylamino ketones is the cyclization of benzalaminoacetals (XVII) (16, 98). The benzal derivative is prepared in 95 per cent yield from the aromatic aldehyde and aminoacetal and is converted to the oxazole by dissolving in sulfuric acid and treating with phosphoric anhydride at 180°C. for 20 min. The only examples which have been described use *o*-nitrobenzalaminoacetal, from which a 45 per cent yield of 2-*o*-nitrophenyloxazole has been obtained, and *p*-nitrobenzalaminoacetal, which has given a 40 per cent yield of 2-*p*-nitrophenyloxazole. It has been stated that this reaction must proceed through oxidation of the CH next to the ring to COH (16).



If an intermediate such as that postulated is formed, its conversion to an oxazole is similar to the conversion of acylamino ketones to oxazoles.

E. FROM DESYL ESTERS AND AMMONIA

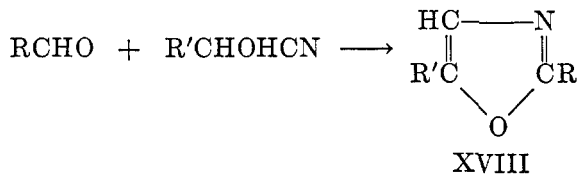
Only two examples of the preparation of oxazoles by the reaction of the ester of an α -hydroxyketone with ammonia have been described. These two are the preparation of triphenyloxazole from desyl benzoate (21) and of 2-methyl-4,5-diphenyloxazole from desyl acetate (21). Yields of 93 and 82 per cent, respectively, were obtained using glacial acetic acid as the reaction medium. This reaction probably proceeds through the enol form of the ester, as follows:



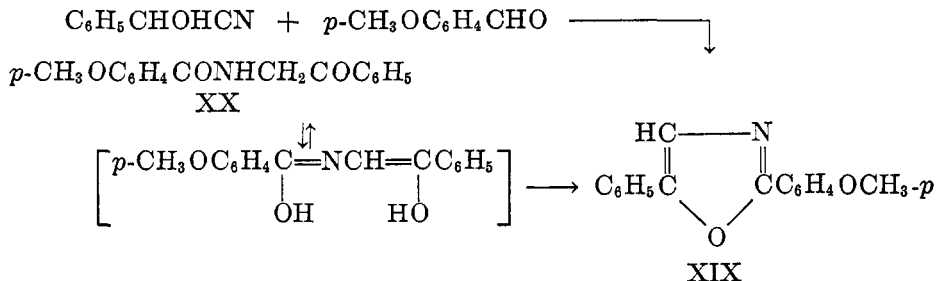
As previously pointed out, this reaction is similar to the preparation of pyrroles from 1,4-dicarbonyl compounds and ammonia.

F. FROM AROMATIC ALDEHYDES AND AROMATIC ALDEHYDE CYANOHYDRINS

In 1896 Emil Fischer (29) found that 2,5-diphenyloxazole hydrochloride was precipitated by passing gaseous hydrogen chloride into an absolute ether solution of benzaldehyde and benzaldehyde cyanohydrin. Many different aromatic aldehydes and cyanohydrin combinations have been converted to 2,5-diaryloxazoles by this procedure in yields of up to 80 per cent (85). The over-all equation can be written as follows:



That the product (XVIII) has the radical of the aldehyde in the 2-position is indicated by the fact that the reaction of benzaldehyde cyanohydrin and anisaldehyde gives the same product (XIX) that is obtained by the dehydration of ω -*p*-methoxybenzoylaminoacetophenone (XX) (78).



As discussed previously, the dehydration reaction is one which proceeds under mild conditions where a rearrangement of the groups would not seem probable, and it is concluded therefore that the product is the 2-*p*-methoxyphenyl-5-phenyloxazole. It has also been observed that the product obtained from anis-

TABLE 3
Oxazoles from aromatic aldehydes and cyanohydrins

ALDEHYDE RADICAL (SUBSTITUENT IN 2-POSITION)	CYANOHYDRIN RADICAL (SUBSTITUENT IN 5-POSITION)	YIELD OF OXAZOLE	REFERENCE
		<i>per cent</i>	
Phenyl	Phenyl	40, 58	(29, 53, 85, 96)
<i>p</i> -Methoxyphenyl	Phenyl	40	(78, 83, 85)
<i>p</i> -Isopropylphenyl	Phenyl		(83)
β -Styryl	Phenyl		(78, 83)
<i>p</i> -Tolyl	Phenyl	*	(85)
3,4-Methylenedioxyphenyl	Phenyl	*	(85)
<i>o</i> -Nitrophenyl	Phenyl	*	(85)
<i>m</i> -Nitrophenyl	Phenyl	*	(85)
<i>p</i> -Nitrophenyl	Phenyl	*	(85)
<i>o</i> -Chlorophenyl	Phenyl	*	(85)
<i>m</i> -Chlorophenyl	Phenyl	*	(85)
Furyl	Phenyl	80	(86)
Phenyl	Methyl	0	(29, 96)
Phenyl	<i>p</i> -Methoxyphenyl		(78, 83)
<i>p</i> -Methoxyphenyl	<i>p</i> -Methoxyphenyl		(53, 79, 83, 84)
<i>p</i> -Isopropylphenyl	<i>p</i> -Methoxyphenyl		(83)
β -Styryl	<i>p</i> -Methoxyphenyl	20	(78, 83)
<i>p</i> -Tolyl	<i>p</i> -Methoxyphenyl	*	(85)
3,4-Methylenedioxyphenyl	<i>p</i> -Methoxyphenyl	*	(85)
<i>o</i> -Nitrophenyl	<i>p</i> -Methoxyphenyl	*	(85)
<i>m</i> -Nitrophenyl	<i>p</i> -Methoxyphenyl	*	(85)
<i>o</i> -Chlorophenyl	<i>p</i> -Methoxyphenyl	*	(85)
<i>m</i> -Chlorophenyl	<i>p</i> -Methoxyphenyl	*	(85)
Phenyl	β -Styryl		(31)
3,4-Methylenedioxyphenyl	3,4-Methylenedioxyphenyl		(42)
<i>m</i> -Nitrophenyl	<i>m</i> -Nitrophenyl		(53)
<i>p</i> -Nitrophenyl	<i>p</i> -Nitrophenyl		(53)
Phenyl	<i>p</i> -Nitrophenyl		(85)
Phenyl	Furyl	60	(86)
Phenyl	<i>p</i> -Tolyl	*	(85)
<i>p</i> -Methoxyphenyl	<i>p</i> -Tolyl	*	(85)

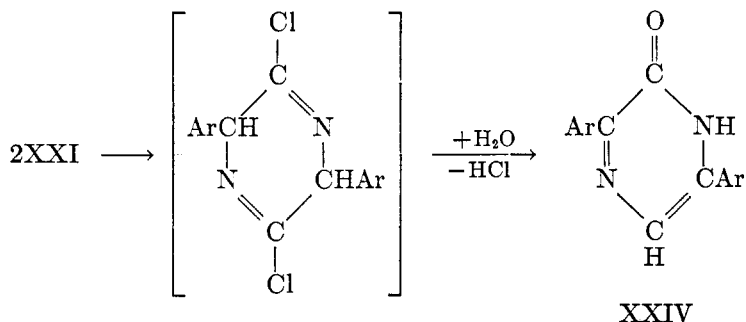
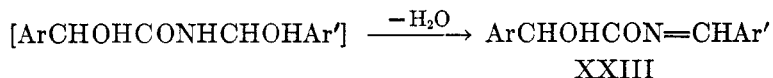
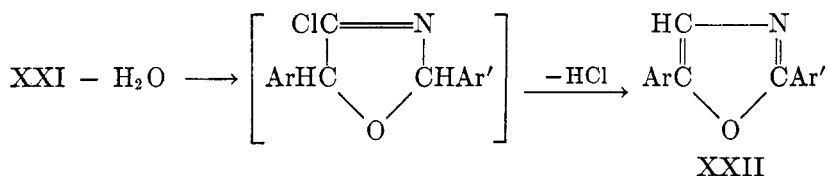
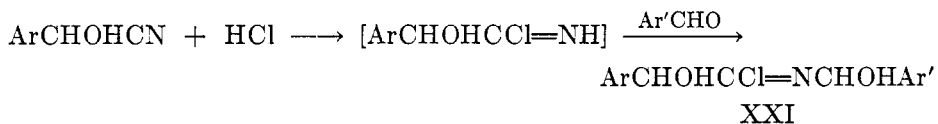
* All yields are 80 per cent.

aldehyde cyanohydrin and benzaldehyde is the same as that obtained from ω -benzoylamino-*p*-methoxyacetophenone, and for similar reasons the product is taken to be 2-phenyl-5-*p*-methoxyphenyloxazole. With mixtures of cinnamaldehyde cyanohydrin and benzaldehyde or of benzaldehyde cyanohydrin and cinnamaldehyde it has been noted that the product which is obtained is an in-

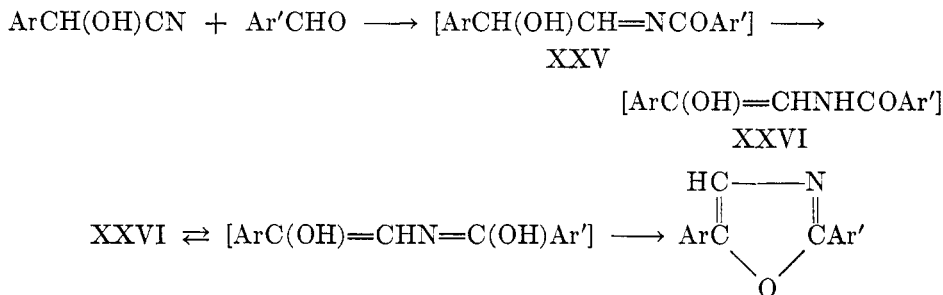
separable mixture of the two isomers (31). This is attributed to an interchange between the cyanohydrin and aldehyde molecules which makes both pairs of reactants available for reaction from either pair of starting materials. An example such as this, where the reaction takes an unexpected course, is sufficient to warrant a critical examination of the structures assigned to the products isolated from other reaction mixtures. With the benzaldehyde-anisaldehyde reactions discussed above, distinct, homogeneous products have been obtained from the two pairs of reactants and the structures as given are probably acceptable.

The various combinations of aldehydes and cyanohydrins that have been used in this reaction are listed in table 3, along with the product isolated and the yield where given. The reaction is carried out in all cases by dissolving the reactants in dry ether and passing in dry, gaseous hydrogen chloride. The oxazole precipitates as the hydrochloride and can be converted to the free base by addition of water (85) or by boiling with alcohol (29, 83).

Two mechanisms have been proposed for this reaction. Ingham (53) has proposed the following sequence of reactions to explain the formation of the three types of products that have been isolated: (a) oxazoles (XXII), (b) arylenemandeloamides (XXIII), and (c) diazines (XXIV) (53, 57):



Whitmore (118) proposes a process that embodies addition of the aldehyde hydrogen to the carbon of the nitrile group to give XXV, a tautomeric shift to XXVI, and dehydration after enolization to form the ring.



Some questions are raised by these two proposals. In the first place it is not understood why acetaldehyde cyanohydrin and benzaldehyde give lactobenzylideneamide but no oxazole. As negative evidence this does not create a serious objection to either mechanism, but it does remain unexplained. A second point to be noted is that the intermediate (XXVI) of the Whitmore mechanism is where Ar and Ar' are phenyl, benzoylaminoacetophenone (VIII, where R and R' are phenyl). This is a compound whose conversion to 2,5-diphenyloxazole has already been noted and, if it is an intermediate, it should be possible either to detect it in the reaction mixture or to convert it to the oxazole by the ether-hydrogen chloride treatment used for this synthesis instead of the sulfuric acid or phosphorus pentachloride treatments usually used in the conversion. There is one other point. Schuster (104) has reported that hydrogen chloride in ether solution converts mandelobenzylideneamide to a compound that must be 2,5-diphenyloxazole hydrochloride on the basis of the properties described, although he has written it as the 2,4-derivative. If this conversion can be verified, it would appear that amides of this type can be intermediates in the reaction and are not necessarily by-products and require an explanation as such.

G. FROM AMIDES AND α -HALOKETONES AND α -HALOALDEHYDES

The preparation of oxazoles from amides and α -haloketones and α -haloaldehydes is similar to the preparation of thiazoles from thioamides and α -haloketones and α -haloaldehydes. The oxazoles, as compared to the thiazoles, are formed in lower yields and at higher temperatures. With the oxazoles it is customary to heat the reactants at 120°C. for 1 to 2 hr., while the thiazoles are readily formed on gentle warming. In some cases the yields are so low that isolation of the oxazole is itself a major problem. This is illustrated by the preparation of 2,4-dimethyl derivatives from chloroacetone. With acetamide a 7 per cent yield of oxazole is obtained (90), while with thioacetamide a yield of about 60 per cent is reported (45). There is the same contrast in the yields of heterocycle from urea and thiourea. A 7 per cent yield of 2-aminoöxazole is obtained with the former and α,β -dichloroethyl ether (2, 3), while thiourea and this ether give nearly theoretical yields of 2-aminothiazole (113). The best

yield reported for the formation of an oxazole by this method is the 55 per cent yield of 2,5-diphenyloxazole obtained from benzamide and phenyl- α -bromoacetaldehyde (29). The difficulties involved in this synthesis can also be seen in the fact that it has been used in the preparation of but ten oxazoles since it was first reported by Blümlein in 1884 (13). These compounds and the starting materials used in their preparation are listed in table 4.

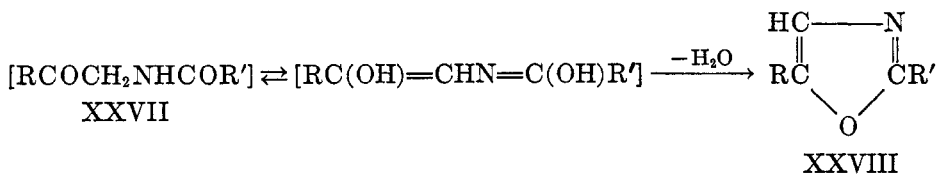
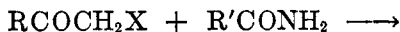
Two mechanisms have been proposed for this reaction (43, 76). If a condensation takes place between the carbon atom alpha to the carbonyl and the nitrogen of the amide through loss of halogen acid, an intermediate acylamino ketone

TABLE 4
Oxazoles from halocarbonyl compounds and amides

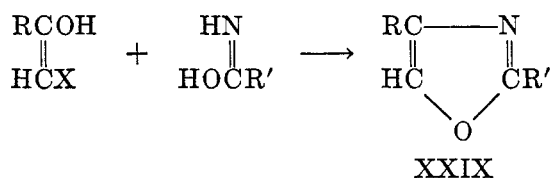
OXAZOLE	α -HALO COMPOUND	AMIDE	REFERENCE
2-Methyl-4-phenyl-	Bromoacetophenone	Acetamide	(13, 43, 75, 76)
4-Phenyl-	Bromoacetophenone	Formamide	(13, 43, 75, 76)
2,4-Phenyl-	Bromoacetophenone	Benzamide	(13, 43, 75, 76)
2,4-Dimethyl-	Chloroacetone	Acetamide	(77, 90, 108)
*	Chloroacetone	Formamide	(77)
2-Phenyl-4-methyl-	Chloroacetone	Benzamide	(77)
2-Phenyl-4-methyl-	Bromoacetone	Benzamide	(33)
2-Phenyl-4,5-dimethyl-	α -Chloroethyl methyl ketone	Benzamide	(33)
2- <i>m</i> -Nitrophenyl-4,5-dimethyl-	α -Chloroethyl methyl ketone	<i>m</i> -Nitrobenzamide	(33)
2,5-Diphenyl-	Phenyl- α -bromoacetaldehyde	Benzamide	(29)
2-Amino-	Bromoacetaldehyde	Urea	(2, 3)
2-Amino-	α - β -Dichlorodiethyl ether	Urea	(2, 3)
2-Amino-5-phenyl-	Bromoacetophenone	Monosodium cyanamide	(34)
*	Bromoacetal	<i>o</i> -Nitrobenzamide	(16)

* No oxazole was obtained.

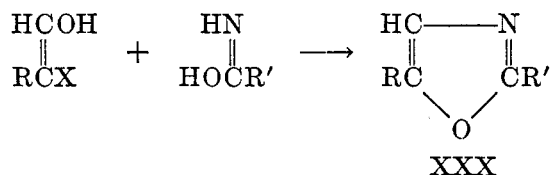
(XXVII) would be formed which on dehydration, in the case of an α -halogen ketone, would form a 2,5-disubstituted oxazole (XXVIII).



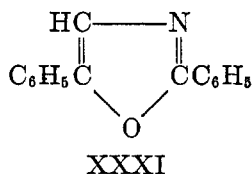
This possibility has been discarded in favor of a mechanism involving a condensation of the enol forms of the amide and halocarbonyl to give, from a haloketone, a 2,4-disubstituted oxazole (XXIX).



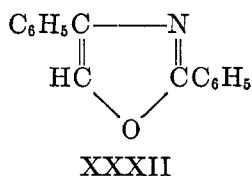
or, from a haloaldehyde, a 2,5-disubstituted oxazole (XXX).



The reason for adopting this mechanism is, as Robinson (96) points out, that the same oxazole is obtained (a) from the reaction of phenyl- α -bromoacetaldehyde and benzamide and (b) by the dehydration of benzoylaminoacetophenone (VIII, where R and R' are phenyl). The latter reaction has been previously discussed and is considered to lead unequivocally to 2,5-diphenyloxazole (XXXI).



It is, therefore, concluded that the reaction of phenyl- α -bromoacetaldehyde and benzamide gives 2,5-diphenyloxazole also and that the product of this reaction cannot be 2,4-diphenyloxazole, as required by the abandoned mechanism. A different diphenyloxazole is formed from bromoacetophenone and benzamide, and it is considered to be the 2,4-diphenyloxazole (XXXII).



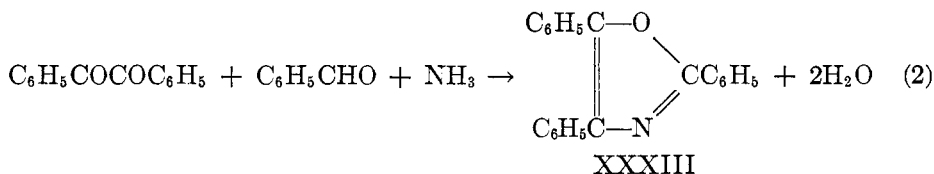
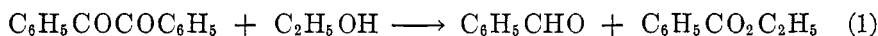
The analogous reaction leading to thiazoles is considered to take a similar course, in which 2,4-disubstituted derivatives are formed from α -haloketones.

H. FROM BENZIL

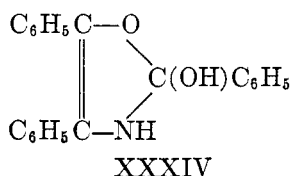
If benzil is treated with ammonia in any one of a number of procedures a reaction takes place with the formation of a mixture of products from which 2,4,5-triphenyloxazole (XXXIII), which has also been called azobenzil by Zinin (126) or benzilam by Laurent (70), can be isolated in yields up to 90 per cent

(102). The reaction is complex, and the type and relative amounts of products are dependent on the conditions used. The products which have been isolated from the reaction under the various conditions include, besides 2,4,5-triphenyloxazole, benzilimide, shown to be *N*-desylbenzamide (XL) (20), and imabenzil, for which various structures (XXXV, XL) have been proposed (20). Both of these can be converted to 2,4,5-triphenyloxazole. Ethyl benzoate (55, 126), ammonium benzoate (102), benzamide (49, 71, 125), a tetraphenylpyrazine derivative (71), diphenylacetylene, diureine when urea is present (11), diphenylimidazole when formaldehyde is present (91), and lophine or 2,4,5-triphenylimidazole (71) have also been isolated.

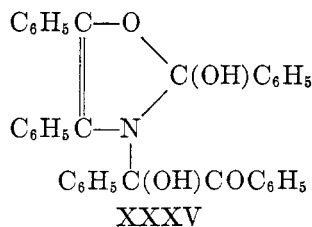
The mechanism of this reaction has been considered carefully by Japp (55, 56) and by Davidson, Weiss, and Jelling (20). The former proposed an initial cleavage of the benzil to give benzaldehyde and ethyl benzoate (equation 1), followed by a condensation of the benzaldehyde with benzil and ammonia (equation 2):



Japp suggested that benzilimide had the structure shown in formula XXXIV

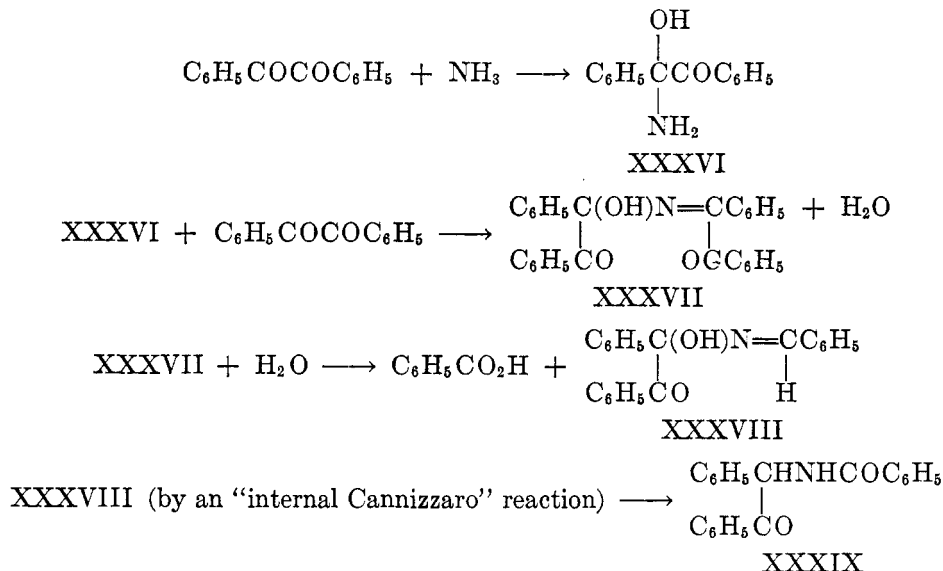


but did not propose any structure for imabenzil. It has since been proposed, on the basis of Japp's mechanism (91), that imabenzil has the following structure (XXXV):

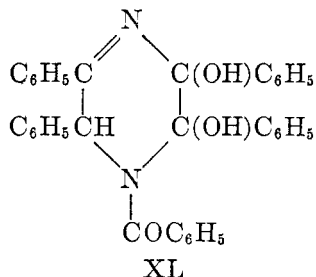


Japp's mechanism was rejected as improbable by Davidson, Weiss, and Jelling (20), because it has been shown by Radziszewski (92) that benzil, benzaldehyde, and ammonia react in alcohol to give essentially quantitative yields of lophine. This weakness in his mechanism was recognized by Japp himself. An alterna-

tive mechanism was proposed by Davidson *et al.* that did not require benzaldehyde as an intermediate. It was suggested that an addition compound (XXXVI), formed from ammonia and benzil, reacted with an additional molecule of benzil to give a condensation product (XXXVII) that was hydrolyzed and rearranged to give *N*-desylbenzamide (XXXIX), as follows:

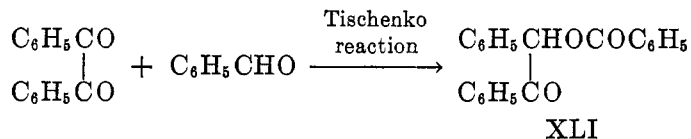


N-Desylbenzamide was shown to be identical with benzilimide. Its essentially quantitative dehydration to triphenyloxazole had already been described by McKenzie and Barrow (81), who did not realize that they were working with the compound known as benzilimide, and its reaction with ammonia is known to give lophine (20). It was further proposed that two moles of *N*-desylbenzamide underwent a reversible condensation to give a pyrazine derivative (XL), which was proposed as the structure for imabenzil.



This mechanism has been questioned recently by Leslie and Watt (71), who point out that in liquid ammonia the Radziszewski imidazole synthesis gives only a 46 per cent yield of lophine and that as a result it is not necessary to postulate the absence of benzaldehyde during the formation of triphenyloxazole,

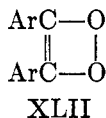
at least in liquid ammonia systems. If the primary formation of benzaldehyde from benzil is granted, the formation of oxazoles can be explained by assuming a Tischenko type of reaction (112) between benzil and benzaldehyde to give a desyl ester (XLI) which, as has been discussed, is known to react with ammonia to form an oxazole (21).



It may also be mentioned in connection with the mechanism of this synthesis that the reaction product from benzil monoxime and benzaldehyde is an oxidoxazole which has been reduced to triphenyloxazole (103). This formation of the oxazole nucleus suggests the possibility that benzil monoimine, $\text{C}_6\text{H}_5\text{COC}(=\text{NH})\text{C}_6\text{H}_5$, is an intermediate in the synthesis from benzil and that an aldehyde is really taking part in the reaction.

In addition to ammonia the following nitrogen-containing compounds react with benzil under the conditions indicated to form triphenyloxazole: urea at 170°C. in ethanol to give a 70 per cent yield (11); benzyhydroxylamine (4); and ammonium formate at 222°C. to give a 70 per cent yield (72). Ammonia has been used (a) without other media at room temperature, 35°C., 103°C., and 200°C. (71, 111), (b) dissolved in absolute alcohol (20, 70), (c) in 30 per cent aqueous solution with alcohol at room temperature and at 130°C. (49), (d) in aqueous solution with alcohol and formaldehyde (91), and (e) in concentrated aqueous solution at 120°C. (102). Of these various systems (e) gives a 90 plus per cent yield of triphenyloxazole and (c) gives an 80–90 per cent yield of imabenzil at room temperature.

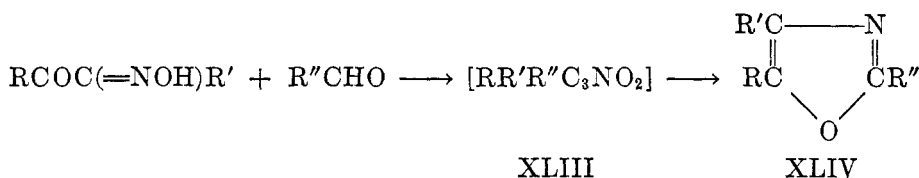
No comprehensive studies have been made to determine the scope of this synthetic method. It has been observed that no reaction occurs when the ammonia is replaced by amines (125) and this is to be accounted for in any mechanism of the reaction. Schönberg and Schönberg and Kramer (102, 103) have demonstrated that concentrated ammonium hydroxide at 120°C. gives over 90 per cent yields of triphenyloxazole or the substituted triphenyloxazole from benzil, 4,4'-dimethylbenzil, 4,4'-dimethoxybenzil, and 3,4,3',4'-bismethylenedioxybenzil, while under the same conditions 4,4'-diethoxybenzil, 2,2'-dimethoxybenzil, and 2,2'-dimethoxy-5,5'-dimethylbenzil give little or no oxazole. The former group of benzils are distinguished from the latter in that they are yellow rather than colorless solids and are more reactive. The colorless compounds are considered to exist as superoxides (XLII) to account for the different reactivity (97).



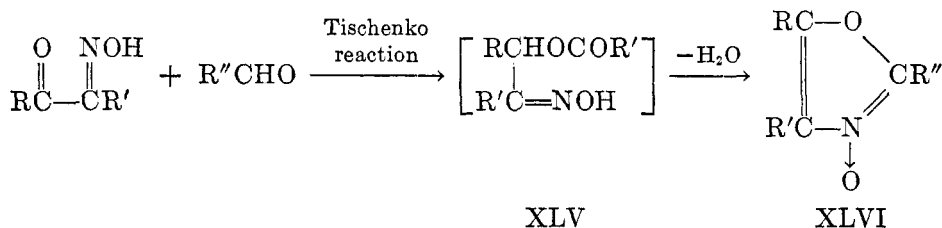
There is an account of a reaction between phenylglyoxal and amino acids which is said to give triphenyloxazole, and the reaction may be analogous (66). No report has been found in which 1,2-diketones of the aliphatic series have been used.

I. BY REDUCTION OF OXIDOÖXAZOLES

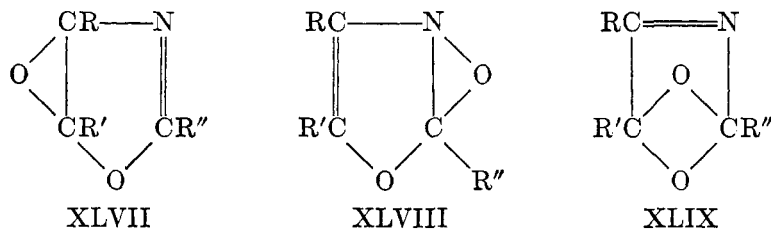
Aldehydes react with the monoximes of 1,2-diketones to form oxidoöxazoles (XLIII) whose structure has not been completely established but which can be reduced to oxazoles (XLIV).



There is little information to indicate what course this reaction takes. The relation between this synthesis and the preparation of oxazoles from benzil and ammonia has been mentioned previously. As with the benzil synthesis, it is possible that the first step in this reaction is a Tischenko reaction in which an oximino ester (XLV) is formed which in turn enolizes and loses water to give the oxidoöxazole (XLVI).



Other possible structures which have been suggested for the oxidoöxazoles (XLVII, XLVIII, and XLIX) will be discussed subsequently.



This reaction was first observed by Diels and Riley (23) in 1915 and has been further studied by Dilthey and Friedrichsen (24). Biacetyl, benzil in its two geometric forms, and acetylbenzoyl monoximes form oxidoöxazoles with a variety of aromatic aldehydes. No aliphatic aldehydes have been used. The reaction is carried out by shaking the reactants with hydrochloric acid (23)

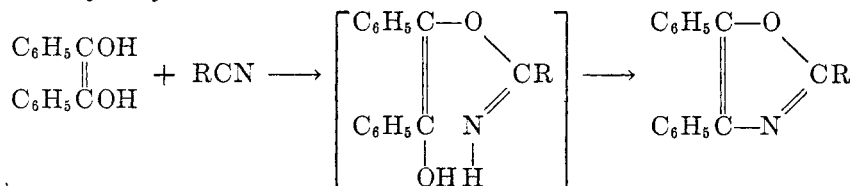
or with acetic acid containing hydrogen chloride (24) to give reported yields of the oxido compound ranging from 60 per cent to quantitative. The reduction to the oxazole, which is accomplished with zinc in water (23) or zinc in acetic acid (24) in yields of 80 per cent, has been demonstrated with the appropriate oxido compounds to give 2,4,5-triphenyloxazole (azobenzil), 2-phenyl-4,5-dimethyloxazole, 2-(4-methoxyphenyl)-4,5-dimethyloxazole, and 2-(4-methoxyphenyl)-4-methyl-5-phenyloxazole. Oxidooxazoles have been prepared using the reactants listed in table 5.

TABLE 5
Reactants in the preparation of oxidooxazoles

OXIME	ALDEHYDE	REFERENCE
Biacetyl.....	<i>p</i> -Methoxybenzaldehyde	(23, 24)
	Benzaldehyde	(23, 24)
	<i>o</i> -Hydroxybenzaldehyde	(24)
	3,4-Methylenedioxybenzaldehyde	(24)
	<i>m</i> -Nitrobenzaldehyde	(24)
	<i>p</i> -Nitrobenzaldehyde	(24)
	Cinnamaldehyde	(24)
Acetylbenzoyl.....	<i>o</i> , <i>p</i> -Dihydroxybenzaldehyde	(24)
	Benzaldehyde	(24)
	<i>p</i> -Methoxybenzaldehyde	(24)
	<i>o</i> -Hydroxybenzaldehyde	(24)
	3,4-Methylenedioxybenzaldehyde	(24)
	<i>m</i> -Nitrobenzaldehyde	(24)
	<i>o</i> -Nitrobenzaldehyde	(24)
Benzil (alpha).....	<i>p</i> -Nitrobenzaldehyde	(24)
	Benzaldehyde	(24)
	<i>p</i> -Methoxybenzaldehyde	(24)
Benzil (beta).....	<i>m</i> -Nitrobenzaldehyde	(24)
	Benzaldehyde	(24)

J. FROM BENZOIN AND NITRILES

The reaction between benzoïn and nitriles to give oxazoles is carried out by adding a mixture of the two reactants to concentrated sulfuric acid with cooling (58). Yields of 30 per cent of 4,5-diphenyloxazole are obtained with hydrogen cyanide, while acetonitrile, propionitrile, and benzonitrile can be used with comparable results. The reaction is considered to proceed through the enol form of benzoïn and may involve addition to the carbon-nitrogen triple bond, followed by dehydration.



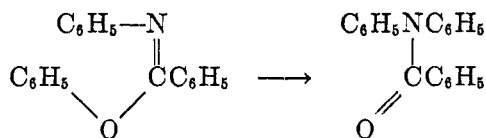
III. PROPERTIES

The properties of the oxazole ring structure are related to those of other heterocyclic rings containing nitrogen and oxygen atoms. The heteroatoms of the oxazole ring are structurally similar to the oxygen in furan and the nitrogen in pyridine, and a behavior intermediate between that of the furans and the pyridines is in fact observed. The oxazoles have basic properties similar to those of pyridines and in some respects show the highly developed aromaticity of the pyridines. At the same time they are less resistant toward oxidation and somewhat more sensitive to acids than the pyridines, as if they had some of the instability of the furans. In order to illustrate the relation between the oxazoles and the furans or the pyridines, comparisons can be made of the severity of the conditions under which various reactions of these ring systems take place. It is unfortunate that reactions under closely similar conditions with analogous derivatives are not always available for the purposes of these comparisons. In the absence of such data, reactions of closely related types have been selected in order to compare, as best as possible, the behavior of the oxazoles with that of the furans and the pyridines. It is to be noted, however, that the oxazoles are compounds which possess aromatic properties of their own characteristic type and that the evidence for this characteristic aromaticity is to be found in an examination of their reported physical and chemical properties.

A. PHYSICAL PROPERTIES

The oxazoles are thermally stable compounds which vary from extremely volatile liquids to those which boil undecomposed at remarkably high temperatures. 2,5-Dimethyloxazole is a liquid at room temperature; it boils at 117°C., is volatile with steam, and can be lost by volatilization on evaporation of ether solutions (122). As larger substituents are introduced the boiling point is raised, as can be seen in the values given in table 6. The 2,4-disubstituted derivatives boil lower than their 2,5-disubstituted isomers. The di- and triphenyl derivatives, all of which melt below 115°C., have boiling points of 340°C. or over and can be boiled at these temperatures without decomposition (55, 56, 58, 70, 75). This behavior is comparable to that of triphenylamine, which can be distilled at a temperature of 350°C. without decomposition. Outstanding thermal stability has also been noticed with 2-methyl-4-phenyloxazole (13, 75), 4-phenyloxazole (75), 2-phenyl-5-methyloxazole (36), and 2-methyl-5-phenyloxazole (36). All of these oxazoles can be boiled or distilled without decomposition at the boiling temperatures listed in table 6. Many of the oxazoles in table 6, but not 2,5-diphenyloxazole, have been steam-distilled (13, 29, 33, 36, 75, 77, 83, 98, 122). The thermal stability of the oxazoles made possible vapor-density determinations with benzilam, and these were instrumental in formulating the structure of the compound as 2,4,5-triphenyloxazole (55, 56).

In view of the fact that the $\text{—N}=\overset{\text{O}}{\underset{\text{O}}{\text{C}}}\text{—}$ system in the open-chain *N*-substituted imino ethers, such as *N*-phenylbenziminophenyl ether, undergoes a rearrangement at 200–300°C. to disubstituted amides (17),



the thermal stability of the oxazoles, which also contain the same $-\text{N}=\text{C}-\text{O}-$ system, is evidence that the properties of the oxazoles are not those of such related open-chain compounds but are rather those of a more stable, less reactive, or "aromatic" compound.

The odor of the oxazoles varies with the type of substituents in the ring. 2-Phenyloxazole is reported to have the odor of methyl salicylate (16), 4,5-

TABLE 6
Melting and boiling points of oxazoles

OXAZOLE	MELTING POINT	BOILING POINT	REFERENCE
	°C.	°C.	
2,4-Dimethyl.....		108	(108)
2,5-Dimethyl.....		117	(122)
2,4,5-Trimethyl.....		134	(122)
2,5-Dimethyl-4-isopropyl.....		160	(122)
2,5-Dimethyl-4-isobutyl.....		180	(122)
2,5-Dimethyl-4-benzyl.....		267	(122)
4-Phenyl.....	6	220	(75)
2-Methyl-4-phenyl.....	45	241	(75)
2-Phenyl-5-methyl.....		254 at 734 mm.	(36)
2-Methyl-5-phenyl.....	58	255 at 748 mm.	(36)
4,5-Diphenyl.....	44	192 at 15 mm.	(58)
2,4-Diphenyl.....	102	339	(75)
2,5-Diphenyl.....	74	Over 360	(29)
2,4,5-Triphenyl.....	115	Over 357	(58)
2-Methyl-5-ethoxy.....		60 at 18 mm.	(63)
2-Phenyl-5-ethoxy.....		150 at 12 mm.	(63)

diphenyl- and 2-methyl-4,5-diphenyl-oxazoles the odor of pepper (58), 2,5-dimethyl-4-benzylloxazole the odor of rose oil (122), 2,4-dimethyloxazole and 2,4,5-trimethyloxazole the odor of pyridine (122), 2,4-dimethyloxazole the odor of 2,4-dimethylthiazole (108), 2,5-dimethyl-4-isopropylloxazole the odor of rotten meat (122), 2,5-dimethyl-4-isobutylloxazole the odor of peppermint (122), and 2-phenyl-5-ethoxyloxazole the odor of ethyl benzoate (63). The oxazoles are insoluble in water, with the exception of 2-methyl-5-ethoxyloxazole (63) and of 2,4- and 2,5-dimethyloxazoles (108, 122), are slightly soluble in ligroin, and are soluble in acetic acid, benzene, alcohol, and ether.

Certain of the oxazoles, some as solids or in solution, others only in solution, show a strong violet to blue fluorescence. The fluorescence is often observed in ordinary light but sometimes only in ultraviolet light, as from burning magnesium or strong sunlight. The largest group of these oxazoles is that of the 2,5-diaryl-

substituted oxazoles, and Robinson has made an extensive study of the effect of various substituents on the intensity of their fluorescence (31, 42, 78, 96). In the 2,5-diphenyloxazole series the introduction of a nitro group destroys while the introduction of methoxyl, methyl, and amino groups intensifies the fluorescence. Thus 2,5-diphenyloxazole does not fluoresce by ordinary light but does in ultraviolet light, while 2-(*p*-aminophenyl)-5-phenyloxazole fluoresces by ordinary light. A greater intensification is observed when a phenyl substituent is replaced by β -styryl or naphthyl. 2- α -Naphthyl-5-phenyloxazole is a yellow, fluorescent solid which fluoresces with phenomenal brilliance when its solution is exposed to ultraviolet light. 2-Phenyl-5- β -styryloxazole is also fluorescent in the solid state (31). The intensity of fluorescence is also determined by the position of the substituent, since 2-phenyl-5- α -naphthyloxazole is not fluorescent in the solid state and is less intensely fluorescent in solution than is 2- α -naphthyl-5-phenyloxazole. The substitution of a benzyl group for either the 2-phenyl or the 5-phenyl group destroys all fluorescence. 2-(*o*-Aminophenyl)oxazole is fluorescent by daylight in solution (16) and 2-(*p*-aminophenyl)oxazole fluoresces on exposure of its alcohol solution to ultraviolet light (98). The last two are examples of fluorescent oxazoles containing only one substituent. 2,4,5-Triphenyloxazole is feebly fluorescent (81), and the carmine dye obtained from 2-(*o*-aminophenyl)-5-phenyloxazole and R salt shows a blue fluorescence (78).

A measurement made with 2-methyl-4,5-diphenyloxazole has shown that this molecule has a rather small dipole moment, which is an indication of resonance contributions from possible polar structures (89). The specific and molecular refractions and dispersion for five oxazoles have been determined by Auwers and Ernst (5). A depression such as that observed with other heterocyclic compounds was observed with 2,4- and 2,5-dimethyloxazoles, while with 4-phenyl-, 5-phenyl-, and 2,5-diphenyl-oxazoles an exaltation, particularly high with the last, was observed.

B. CHEMICAL PROPERTIES

The nature of the substituents in the oxazole ring makes a great difference in the properties of the various oxazole derivatives. In particular, such properties as basicity and stability of the ring toward hydrolytic reagents are profoundly modified. The variation is great enough to require a careful analysis of the facts in making general conclusions. There is for instance the generalization, met in those textbooks which discuss the oxazoles (62b, 94), that the oxazole ring is readily split by acid hydrolysis. This is true in specific instances, as in the case of the alkoxyoxazoles (63), but is not at all general, since it has been shown that in some cases the oxazoles are remarkably stable to aqueous acids. 2,5-Dimethyloxazole can be recovered quantitatively after treatment with 15 per cent hydrochloric acid at 100°C. for 6 hr. (122), and 2,5-diphenyloxazole is not altered by strong hydrochloric acid after several hours at 150°C. (29). Such facts, rather than indicating a facile acid hydrolysis, indicate a considerable resistance toward acids. The following discussion will be concerned with pre-

senting illustrative facts upon which an appraisal of the chemical behavior of the oxazoles can be based.

1. Basicity

The oxazoles are weak bases, and their basic properties are similar to those of other weak amines in general and to those of pyridine in particular. All of the known oxazoles form salts with acidic reagents of one type or another, and this serves to establish a basic character. An indication of the weak basicity can be seen in the fact that 2,5-dimethyloxazole fails, as does pyridine, to turn red litmus blue (122). Since there are no available data on their basic dissociation constants the solubility of the oxazoles in aqueous acid and the stability of the oxazole hydrochlorides toward hydrolysis will be discussed as a means of evaluating the basicity of the oxazoles.

The oxazoles can be divided into two groups on the basis of their solubility in aqueous acid. One includes those soluble in dilute acid, while the other includes those soluble in concentrated but insoluble in dilute acid. The oxazoles which fall in the former class include the water-soluble 2,4-dimethyl-, 2,5-dimethyl-, and 2,4,5-trimethyl-oxazoles (108, 122), the water-soluble 2-methyl-5-ethoxyoxazole (63), 2,5-dimethyl-4-isobutyloxazole (122), and 2-amino-5-phenyloxazole (34). With the lower alkyl- and alkoxy-oxazoles the solubilities in water and in dilute acid cannot be separated. Increased basicity is indicated with the alkyloxazoles by the dilute acid solubility of the closely related water-insoluble 2,5-dimethyl-4-isobutyloxazole. The dissociation of the hydrochloride of 2-methyl-4-isobutyl-5-ethoxyoxazole (63) by water indicates that the lower alkoxyoxazoles are merely water-soluble and not of increased basicity. With the amino-substituted phenyloxazole an increase in basicity is apparent from the fact that the greater number of aryl-substituted oxazoles are insoluble in dilute acid. It has already been noted in connection with the preparation of oxazoles from acylaminocarbonyl compounds that the aryloxazoles precipitate as the free base on dilution of the concentrated sulfuric acid solutions of the oxazoles obtained in the reaction. This property is displayed in other acids, and a compilation of the compounds which have been reported to behave in this fashion is made in table 7 along with the acids in question. 2-Phenyl-5-veratryloxazole is exceptional in that its hydrochloride is not dissociated by water (96).

The ease with which the hydrochlorides of the oxazoles are decomposed is related to their weak basicity. The hydrochlorides of the oxazoles, whose preparation will be discussed later, when dissolved in absolute alcohol and the solution boiled, precipitate as the free oxazoles. As a result the hydrochlorides are best crystallized from alcohol containing dissolved hydrogen chloride. This behavior was first noted by Emil Fischer (29) in working with 2,5-diphenyloxazole and has been affirmed since then with many 2,5-diaryloxazoles (42, 83, 85, 86) and with alkyl (122) and alkoxy (63) oxazoles. With some oxazoles it is possible to volatilize the oxazole from an acid solution. 2,5-Dimethyloxazole and 2,4,5-trimethyloxazole are volatilized and can be lost on evaporation

of their acid solutions (122), and 2-methyl-4-phenyloxazole can be steam-distilled from acid solution (75). It has also been noticed that the free base can be precipitated by the addition of water to alcoholic solutions of the hydrochlorides of 2-(*p*-methoxyphenyl)-5-phenyloxazole (83) or 2,5-diphenyloxazole (29) or by the addition of water to the hydrochloride of 2-methyl-4-isobutyl-5-ethoxyoxazole (63) or of 2-phenyl-5-ethoxyoxazole (63). These properties are similar to those shown by such weak bases as diphenylamine and 2,5-diphenylpyrrole, which are also insoluble in dilute acid and form hydrochlorides that are hydrolyzed by water with the precipitation of the free base (30), and are all consistent with the weakly basic character of the oxazoles.

TABLE 7
Oxazoles soluble in concentrated but insoluble in dilute acids

OXAZOLE	ACID				REFERENCE
	H ₂ SO ₄	HCl	HNO ₃	CH ₃ COOH	
2-Phenyl-.....	x				(16)
2-Nitrophenyl-.....	x	x			(16)
2,5-Diaryl-.....	x				(78, 96)
2,5-Diphenyl-.....	x	x	x		(29)
2,4,5-Triphenyl-.....	x	x	x		(49, 72, 70, 81)
4,5-Diphenyl-.....	x				(58)
2-Methyl-4,5-diphenyl-.....	x				(58)
2-Ethyl-4,5-diphenyl-.....	x				(58)
2-Phenyl-4-methyl-.....	x	x			(27)
2- <i>p</i> -Nitrophenyl-.....	x	x			(98)
2,4,5-Tri(nitrophenyl)-.....	x				(114)
2-(4-Methoxyphenyl)-4-methyl-5-phenyl-.....				x	(24)

"x" indicates that solubility in concentrated and insolubility in dilute acid has been reported in the reference given; a blank indicates that the information has not been reported.

2. Salt formation

The tendency of the oxazoles to enter into salt-forming reactions with various reagents is a property that is due to their basic nature. Hydrochlorides are best prepared by passing hydrogen chloride into an absolute ether solution of the oxazole (29, 42, 83, 122), but benzene has also been used as the reaction medium (75). Occasionally the hydrochloride will separate from a concentrated hydrochloric acid solution (63, 78), and there is a report that 2,4-dimethyl-oxazole hydrochloride was obtained by evaporation of a hydrochloric acid solution (108). Other salts which have been prepared are the chloroaurates (7, 36, 114, 122), chloroplatinates (7, 36, 58, 75, 99, 108, 122), mercurichloride (108), chromates (7, 36, 99), sulfates (75, 83), nitrate (83), and picrates (16, 36, 63, 64, 75, 78, 83, 98, 99, 122). Standard procedures are used and failure to obtain the desired salt has been observed in but few cases. One of these is

2-phenyl-5-tolyloxazole, which does not give a chloroaurate, chloroplatinate, or chromate but does give a picrate (99). The picrates are used in the isolation of the 5-alkoxyoxazoles and some special procedures have been devised for handling them (63, 64). A quaternary salt has also been prepared from methyl iodide and 2,5-diphenyloxazole (29, 119), and if this reaction is a general one the oxazoles resemble the pyridines which do rather than the pyrroles which do not (109) form quaternary salts from alkyl halides. Colored solids, which are described as highly birefringent addition compounds, crystallize from an acetic acid solution of 2,5-diphenyloxazole hydrochloride or methiodide on addition of iodine or bromine (119). Although not completely identified, these products are probably perhalides, since the preparation and properties correspond to those of the pyridine perbromides (26). The salt-forming reactions of the oxazoles have been successfully applied in a sufficient number of instances to indicate that the reaction is quite general.

3. Stability toward acids and bases

In their resistance toward ring scission by acid the oxazoles are somewhat more stable than the furans but are less stable than the pyridines. The furans are often polymerized or decomposed by acids (38). 2-Methylfuran is attacked at 105°C. by water made acid with hydrochloric acid and at 120°C. is completely decomposed (48). If this furan is left to stand at room temperature in a methanol solution with hydrogen chloride, decomposition is evidenced within one day by the presence of aldehydes in the solution (48). 2,5-Dimethylfuran and 2,3,5-trimethylfuran can be completely hydrolyzed by 15 hr. shaking with a cold hydrochloric acid prepared from two volumes of acid of sp. gr. 1.175 and one volume of water (32) or by refluxing with very dilute sulfuric acid (12). In contrast with this it has already been noted that 2,5-dimethyloxazole can be quantitatively recovered after 6 hr. treatment with 15 per cent hydrochloric acid at 100°C. and other alkyloxazoles behave similarly (122). As has been pointed out (39), the type of substitution plays an important rôle in the stability of the furans toward ring scission by acid. Negative substituents increase the stability of the furans, and this behavior is paralleled in the increase observed in the stability of the phenyloxazoles noted in table 8. The comparison between 2,5-diphenylfuran and 2,5-diphenyloxazole indicates a greater stability of the latter. The 2,5-diphenylfuran can be dissolved in concentrated sulfuric acid to give a solution which turns brown on warming and shows color reactions typical of diphenacyl (61), while 2,5-diphenyloxazole is not attacked by concentrated hydrochloric acid during 6 hr. at 150°C. (29). In comparison with the pyridine ring the oxazoles are apparently less stable toward scission of the ring. The stability of the pyridine ring toward acids is illustrated by the extreme conditions used in the successful nitration and sulfonation of the ring. Pyridine and its methyl derivatives can be sulfonated at 220–230°C. to give yields of up to 71 per cent of the sulfonic acid (80), and pyridine has been recovered unchanged to the extent of 50 per cent from nitration reactions at temperatures of 300–450°C. (50). The data of table 9 show that some aryl-substituted

oxazoles, such as 2,4,5-triphenyloxazole, are decomposed at much lower temperatures by acids. The conversion of pyridine to ammonia and pentane by hydriodic acid at 300°C. may be cited by way of indicating a limit to the stability with the pyridines (52).

The stability of the oxazole ring toward acid hydrolysis has already been mentioned as a property which needs careful evaluation, and there is an abundance of data to draw on in making such an evaluation. The preparation of oxazoles and their transformations which are carried out in aqueous acid without destroying the oxazole ring will be considered first. The conditions under which the oxazole ring has been opened by acid will be discussed subsequently. The experimental data available indicate that the oxazole ring is not so sensitive to aqueous acid that it is necessary to avoid acid conditions in preparing oxazoles or that it is impractical to carry out transformations of oxazoles involving acidic reagents. The preparation of oxazoles under aqueous acidic conditions has already been discussed. The oxidooxazoles (23, 24), 2,4,5-triphenyloxazole (20, 49, 81), a variety of 2,5-diaryloxazoles (78, 96), and 4,5-diphenyloxazole are examples of oxazoles prepared by various methods all of which use aqueous acid. In addition to being formed in the presence of aqueous acid the oxazoles can undergo reactions in aqueous acid systems without splitting of the ring. The acetyl derivatives of 2-sulfanilamido-5-phenyloxazole and of 2-(*p*-sulfanilamidophenyl)oxazole can be hydrolyzed to the free sulfanilamidooxazoles in dilute hydrochloric acid (8, 98). In the latter case a 95 per cent yield was obtained by refluxing for 30 min. with 12 per cent hydrochloric acid. The oxidooxazoles are reduced to oxazoles in acetic acid with zinc (24). Phenyloxazoles have been nitrated with concentrated (29) and dilute (114) nitric acid to nitrophenyloxazoles, as will be discussed later. The salts of several oxazoles that have been isolated from concentrated acid are 2,4-dimethyloxazole hydrochloride (108), 2-methyl-4-phenyloxazole sulfate (75), 2-phenyl-5- α -naphthyloxazole hydrochloride (78), 5-phenyl-2-(*m*-nitrophenyl)oxazole hydrochloride (78), and some other 2,5-diaryloxazole hydrochlorides (78). Some oxazoles have been subjected to acidic conditions for the express purpose of determining their stability. Specific examples thus tested and the conditions under which the tests were made are given in table 8.

The oxazole ring is split by the action of aqueous acids, and there have been enough reported examples to indicate the conditions under which the reaction occurs. The oxazoles most easily hydrolyzed by acid are the 5-alkoxyoxazoles. Karrer and his collaborators have studied this reaction in detail (40, 63, 64). The most easily hydrolyzed compound of this group is 2-methyl-5-ethoxyoxazole. An aqueous solution of its hydrochloride is completely hydrolyzed after standing 3 days at room temperature (63). The presence of other substituents makes the alkoxyoxazole more resistant to hydrolysis. Thus, 2-*sec*-butyl-4-isobutyl-5-ethoxyoxazole requires 20 hr. heating on the water bath with 10 cc. of water and 5 cc. of concentrated hydrochloric acid (63) and 2-campholyl-4-isobutyl-5-ethoxyoxazole requires 4-5 hr. heating on the steam bath with concentrated hydrochloric acid to complete the hydrolysis (40). Other oxazoles which have

been hydrolyzed or decomposed by heating with acids at high temperatures are listed in table 9, along with the conditions used and the results. Some of these compounds are listed in table 8, and a comparison of the data in the two tables serves to indicate the minimum conditions required for acid decomposition.

The oxazoles are for the most part quite stable toward alkali and in this respect resemble other related cyclic compounds, including the furans (38

TABLE 8
Oxazoles stable to acids

OXAZOLE	CONDITIONS	RESULT	REFERENCE
2,5-Dimethyl- (and others)...	15 per cent HCl, 6 hr., 100°C.	Quantitative recovery of unchanged oxazole	(122)
2-(<i>o</i> -Nitrophenyl)-.....	Concentrated HCl, boil	Recovered much of oxazole unchanged	(16)
2,5-Diphenyl-.....	Concentrated HCl, several hours, 150°C.	Oxazole not altered	(29)
2,4,5-Triphenyl-.....	Concentrated HCl, 240°C.	After long exposure decomposition of oxazole set in	(72)
2,4,5-Tri(nitrophenyl)-.....	Concentrated HCl, 7 hr., 245°C.	Oxazole unchanged	(122)

TABLE 9
Oxazoles decomposed by acids

OXAZOLE	CONDITIONS	RESULT	REFERENCE
2-(<i>p</i> -Nitrophenyl)-4-methyl-...	Constant-boiling HCl, 3 hr., 100°C.	Hydrolyzed	(33)
2-(<i>o</i> -Nitrophenyl)-.....	Concentrated HCl, 150°C.		(16)
2,5-Diphenyl-.....	Fuming HI, 160°C.		(29)
2-(Aminophenyl)-.....	Acid, high temperature		(33)
2-Methyl-4-phenyl-.....	Concentrated HCl, 200°C.	Resinification	(76)
Nitrophenyldiphenyl-.....	Concentrated HCl, 245°C., 3-4 hr.	Completely split	(122)
2,4,5-Triphenyl-.....	Concentrated H ₂ SO ₄ , 250°C.	Benzoic acid, ammonium sulfate, and resin formed	(55)

Such stability is indicated in the types of operations that can be carried out under alkaline conditions without ring scission. Acetyl derivatives of sulfanil-amidooxazoles are hydrolyzed to the free amines with aqueous alkali (8, 60, 98); 2-(aminophenyl)oxazole can be steam-distilled from alkali (33); 2-campholyl-4-isobutyl-5-ethoxyoxazole is not changed by heating for 1 hr. with aqueous potassium hydroxide (40); 2,4,5-triphenyloxazole is unattacked by boiling alcoholic potassium hydroxide (70); 2-methyl-5-phenyloxazole shows no reaction with

alcoholic potassium hydroxide at 200°C. (76) and can be distilled unchanged over glowing soda lime or sodium hydroxide (13, 76); and 2,5-dimethyloxazole is unchanged and can be recovered quantitatively after 6 hr. treatment with 10 per cent sodium hydroxide at 100°C. (122). A reaction with sodium and alcohol will be discussed in connection with the effect of reducing agents. Sodium amalgam and alcohol do not attack 2-methyl-5-phenyloxazole (76).

4. Oxidation

The oxazoles are readily attacked by oxidizing agents such as permanganate in acidic (122), alkaline (122), or neutral (16, 76, 90, 122) solution; chromic acid (29, 49, 55, 83, 114, 125); bromine water (16, 76); hypobromite (41); chlorine in alcohol or acetone (83); and nitric acid (23, 70, 114). These reagents attack oxazoles having either aromatic or aliphatic substituents and the usual result is cleavage of the oxazole ring. Thus, 2,5-diphenyloxazole is oxidized to phenylglyoxalbenzamide ($C_6H_5COCONHCOC_6H_5$) in 70 per cent yield by chromic acid (29, 83) and in 80 per cent yield by chlorine in alcohol (83). 2-Methyl-5-phenyloxazole is oxidized to benzoic acid by neutral permanganate (76). Triphenyloxazole is oxidized quantitatively to benzoic acid and ammonia by chromic acid (55) and to benzil by warm nitric acid of density 1.5 (114). 2-Anisyl-4,5-dimethyloxidooxazole is oxidized by 2 per cent hot nitric acid to diacetyl, methyl or ethyl nitrite, anisic acid, and water (23). The oxazole ring is not oxidized by nitric acid under the conditions used in the nitration of phenyloxazoles and this reaction, which has been used widely, will be discussed in detail in the following section. 2,4-Dimethyloxazole has been reported to give low yields of a compound thought to be 2-methyloxazole-4-carboxylic acid when oxidized by 4 per cent aqueous potassium permanganate (90). By way of comparison it may be stated that the furans are also readily attacked by oxidizing agents such as bromine water or dilute nitric acid (38, 51) and that pyridine, which is fairly stable to cold permanganate, is oxidized rapidly at 70°C. by alkaline (22) and at 100°C. by neutral permanganate (107) and is decomposed by chlorine water (9, 65). These facts indicate that the oxazoles are probably more easily oxidized than the pyridines.

5. Nitration of phenyloxazoles

Oxazoles bearing phenyl substituents can be nitrated under a variety of conditions to give products with a nitro group in the phenyl ring. As can be seen from the data of table 10, the yield of product from 2,5-diphenyloxazole is almost quantitative, while yields of 77 and 90 per cent have been reported with other oxazoles. Such yields demonstrate a stability of the oxazole ring toward oxidation by nitric acid. The data indicate tentatively that the oxazole ring is not as readily nitrated as is the benzene ring. No nitrooxazoles have been isolated from the nitration of phenyloxazoles where the 4- or 5-position of the oxazole ring is open. There is no information on the nitration of oxazoles having no substituent in the 2-position or having no phenyl substituents, so it is premature to draw final conclusions as to the possibility of nitrating the oxazole ring.

If the oxazole ring is analogous to the pyridine ring, extreme conditions will be required for its nitration (80) and it is more than likely that under these conditions the oxazole ring will be oxidized. Amino substituents in the oxazole ring, as in the pyridine ring, should make nitration possible under less vigorous conditions but there is no reported attempt to nitrate any of the known aminooxazoles. This resistance toward nitration is quite the opposite from what one would expect if the oxazoles resembled the easily nitrated (39) or sulfonated (51) furans.

In the nitration of the phenyloxazoles the fact that the nitro group enters the benzene ring para to the position of attachment to the oxazole ring is fairly well established. The nitration products, which behave as pure compounds,

TABLE 10
Nitration of phenyloxazoles

OXAZOLE	CONDITIONS	RESULTS	REFERENCE
2-Phenyl.....	Concentrated H ₂ SO ₄ , KNO ₃ , 70°C.	77 per cent crude 2- <i>p</i> -nitrophenyloxazole	(98)
2-Phenyl-4-methyl.....	3 parts concentrated H ₂ SO ₄ to 2 parts fuming HNO ₃ , 0°C.	90 per cent of 2- <i>p</i> -nitrophenyl-4-methyl-oxazole	(33)
2-Phenyl-4,5-dimethyl.....	3 parts concentrated H ₂ SO ₄ to 2 parts fuming HNO ₃ , 0°C.	50 per cent of 2- <i>p</i> -nitrophenyl-4,5-dimethyl-oxazole	(33)
2-Methyl-5-phenyl.....	Concentrated HNO ₃	Little effect	(76)
2-Methyl-5-phenyl.....	Fuming HNO ₃	Mononitro compound	(76)
2,5-Diphenyl.....	Cold, fuming HNO ₃	Almost quantitative yield of 5-(<i>p</i> -nitrophenyl) - 2 - phenyl-oxazole	(78, 83)
2,5-Dipiperonyl.....	Glacial acetic acid, HNO ₃	Nitro derivative precipitates	(42)
2,4,5-Triphenyl.....	HNO ₃ (d. 1.48)	2-Nitro derivative	(49)
2,4,5-Triphenyl.....	HNO ₃ (d. 1.46), 15°C.	Mononitro derivative	(114)
2,4,5-Triphenyl.....	Repeated treatment with cold HNO ₃ (d. 1.5)	Tri(<i>p</i> -nitrophenyl)-oxazole	(114)
2,4,5-Triphenyl.....	HNO ₃ (d. 1.5), warm	Decomposition	(114)

have been decomposed by treatment with acid (33, 114) or by oxidation (83) to give *p*-nitrobenzoic acid. No *o*- or *m*-nitrobenzoic acid has been found. The nitro compound obtained by nitration of 2,5-diphenyloxazole has been oxidized to *p*-nitrobenzoic acid (83), and since it is not identical with the 2-(*p*-nitrophenyl)-5-phenyloxazole prepared from 2-*p*-nitrobenzoylaminoacetophenone (78), it has been assumed that it is the 2-phenyl-5-(*p*-nitrophenyl)oxazole.

6. Reduction

Typical aromatic stability toward reduction is shown by the oxazoles. It can be seen in the reduction of nitrophenyloxazoles to aminophenyloxazoles,

in the conversion of oxidooxazoles to oxazoles, and in the unsuccessful attempts to reduce some other oxazoles. Eleven nitrophenyloxazoles which have been successfully reduced to aminophenyloxazoles are listed in table 11. Both chemical and catalytic reductions have been successful, and a quantitative yield has been reported by the latter process (98). The isolation of aminophenyl derivatives in which the oxazole nucleus is not changed indicates that the oxazole nucleus carrying phenyl substituents is stable to these various reagents. The reduction of oxidooxazoles (23, 24) by zinc and water or zinc and acetic acid to the corresponding oxazoles, which has already been discussed, may be mentioned here as another example of the stability of the oxazole nucleus to reducing agents. The observations that 2-methyl-5-phenyloxazole is unchanged by treatment with zinc and acetic acid for several hours or with sodium amalgam and alcohol (76) and that 2,5-dimethyloxazole is not reduced over palladium catalyst in either ethanol or acetic acid (122) are further evidence of this stability.

TABLE 11
Nitrophenyloxazoles reduced to aminophenyloxazoles

OXAZOLE REDUCED	CONDITIONS	YIELD OF AMINO-PHENYLOXAZOLE	REFERENCE
2-(<i>p</i> -Nitrophenyl)-.....	Raney nickel, 3 atm., 40 min.	Quantitative	(98)
2-(<i>o</i> -Nitrophenyl)-.....	Raney nickel, 3 atm., 40 min.	97 per cent	(16)
2-(<i>p</i> -Nitrobenzenesulfonamido)-.	FeSO ₄ , NH ₄ OH, boiling water	45 per cent	(1, 3)
2-(<i>p</i> -Nitrophenyl)-4-methyl-....	Fe, water		(33)
2-(<i>m</i> -Nitrophenyl)-4-methyl-....	Fe, water		(33)
2-(<i>p</i> -Nitrophenyl)-4,5-dimethyl-.	Fe, water		(33)
2-Phenyl-5-(<i>p</i> -nitrophenyl)-.....	SnCl ₂ , HCl		(76)
2-(<i>m</i> -Nitrophenyl)-5-phenyl-....	Sn, HCl, boil		(78)
2-(<i>o</i> -Nitrophenyl)-5-phenyl-....	Sn, HCl, 100°C., 30 min.		(78)
2-(<i>p</i> -Nitrophenyl)-5-phenyl-....	Sn, HCl, boil, 30 min.		(78)
Nitrophenyldiphenyl-.....	Zn, HCl, and acetic acid		(114)
Tri(nitrophenyl)-.....	Zn, HCl	None	(114)

Of the oxazoles which have reacted with reducing agents 2,5-diphenyloxazole has been most carefully studied (29) and has been shown to form benzyl(β -phenyl- β -hydroxyethyl)amine, C₆H₅CH₂NHCH₂CHOHC₆H₅, on treatment of an alcoholic solution of its hydrochloride with sodium, and to form benzylamine when treated with hydrogen iodide. Sodium and alcohol attacks 2-methyl-5-phenyloxazole (76) and 2,5-dimethyloxazole (90) with the formation of compounds which may be oxazolidines but which have not been completely identified. Such a reduction would be comparable to the reduction of pyridine and its homologues to piperidine by sodium and alcohol (69, 81a). Hydrogen iodide and red phosphorus also attack 2-methyl-5-phenyloxazole, with the formation of unidentified products (76). Robinson has suggested the generality of the conversion of oxazoles to substituted *N*-ethylamides by hydrogenation over a platinum and palladium catalyst (124).

7. *Unclassified reactions*

A few reactions of the oxazoles which have not been discussed include the conversion of oxazoles to imidazoles by treatment at high temperatures with ammonia. 2-Methyl-4,5-diphenyloxazole (58), 2-phenyl-4-methyloxazole (77), and 2,5-diphenyloxazole (83) have been converted to imidazoles by this reaction. With the first of these only a low yield of imidazole was obtained after treatment with alcoholic ammonia at 300°C. for 6 hr., and most of the oxazole was recovered unchanged. With the last, 1.5 g. of the imidazole was obtained from 2 g. of oxazole after a similar treatment. Tri(nitrophenyl)oxazole could not be converted to the imidazole (114). Suspected sulfonations in the preparation of 2,5-diaryloxazoles have been reported by Robinson (78). The sulfonation of the oxazole ring may be expected to take place readily in view of the ease with which furans can be sulfonated (51), but such behavior would not be consistent with the resistance to nitration noted above. An attempt to condense acetaldehyde with 2,4-dimethyloxazole gave unidentified products (90), and treatment of 2-phenyl-5-ethoxyoxazole with glycerol and barium hydroxide gave a product which had the "characteristic reactions of natural proteins" (88). Reagents which have been reported not to undergo reaction with oxazoles include phenylhydrazine (16, 29, 76), hydroxylamine (76), Schiff's reagent (16), acetic anhydride (43), phosphorus pentachloride (76), glowing zinc (76), glowing sodium hydroxide or soda lime (13, 76), and nitrous acid (29). In most of these cases the oxazole was recovered unchanged and the failure to obtain a reaction is of significance in structure determination since it indicates the absence of characteristic groups such as carbonyl, amino, and hydroxyl.

8. *Pharmacology*

Several oxazoles have been prepared for examination as sulfa derivatives and as local anesthetics, and studies of the toxicity of some oxazoles have been reported. Feuerriegel (27, 122) has reported that subcutaneous injections of 10 mg. of 2,5-dimethyloxazole in 0.5 cc. of water are fatal to mice. With similar injections of 1 mg. and 5 mg. of 2,4,5-trimethyloxazole no effect was observed, but with 10 mg. temporary symptoms were produced and with 20 mg. death resulted after apparent recovery. With 20-mg. injections of 2,5-dimethyl-4-benzyloxazole and 2,5-dimethyl-4-isobutyloxazole in olive oil there was no observed effect other than a drowsiness produced by the former. Such temporary soporific effects may be produced by other types of exposure. Other general studies have been made (25), and it is also reported that 2-(*o*-sulfanilamidophenyl)oxazole is not toxic to mice in dose levels up to 5, 10, and 20 mg. per gram of animal body weight. Feuerriegel has reported that headaches result from inhaling the vapors of the lower-boiling aliphatic substituted oxazoles (122).

The sulfanilamido derivatives have shown some promise as bactericides. 2-Sulfanilamidooxazole "showed a degree of bacteriostasis equal to that of sulfathiazole but in spite of high blood levels was without activity in experimental mouse infections" (3). 2-Sulfanilamido-5-phenyloxazole was observed as "having the same activity as sulfathiazole against pneumococci according to

Kai Schmith" (60). With 2-(*o*-sulfanilamidophenyl)oxazole it was reported that "in staphylococcal infections in mice this compound was not particularly effective in comparison with sulfathiazole. In streptococcal infections, although some activity was shown, the compound was not as effective as sulfanilamide" (98). The 2-aminophenyloxazoles "are local anesthetics but the solutions possess an acidity too high for practical use" (38).

C. PROPERTIES OF SUBSTITUTED OXAZOLES

Only a few of the many possible types of substituted oxazoles have been prepared. These include, in addition to the hydrocarbon-substituted oxazoles, amino-, aminophenyl-, ethoxy-, and chloroöxazoles. The preparation of the aminoöxazoles from urea (2, 3) or sodium cyanamide (34), of the aminophenyl-oxazoles from nitrophenyloxazoles, and of the ethoxyoxazoles from amino acid esters has already been mentioned. Some properties of the derivatives, such as the basicity of the aminoöxazoles and the hydrolysis of the ethoxyoxazoles, have also been mentioned. There are other properties and reactions of these compounds which merit further description.

1. Aminoöxazoles

The 2-aminoöxazoles are readily acylated with acid chlorides, acetic anhydride, or sulfonyl chlorides. The acetyl derivative of 2-amino-5-phenyloxazole is formed in quantitative yields, using acetic anhydride, and the benzoyl derivative can be prepared with benzoyl chloride (34). Sulfanilamidoöxazoles can be prepared from 2-aminoöxazole and 2-amino-5-phenyloxazole. In the former case the amino group was converted to the *p*-nitrobenzenesulfonyl derivative, using the chloride, and then reduced to the sulfanilamide (1, 3). In the latter case the amine was acylated, using acetaminobenzenesulfonyl chloride, and the product hydrolyzed to the sulfanilamide (8, 60). With the exception of the thiourea prepared from 2-amino-5-phenyloxazole and phenyl isocyanate (34), other reactions of the aminoöxazoles remain to be investigated.

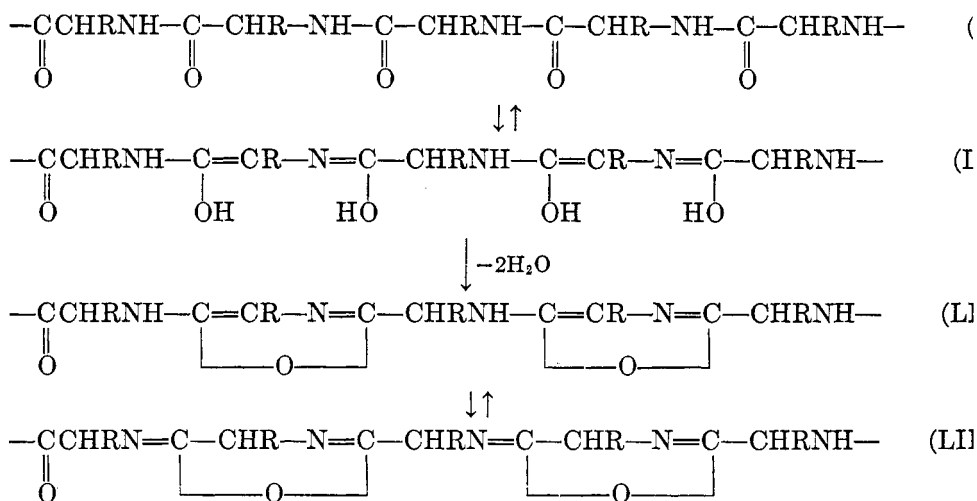
2. Aminophenyloxazoles

The aminophenyloxazoles have been examined in a number of reactions, and their behavior has been found to be quite similar to that of other aniline derivatives. Acetyl, benzoyl, and sulfonamido derivatives have been prepared from acyl chlorides (16, 98). The fluorescence observed with other oxazoles has also been observed with aminophenyloxazoles (78, 98). Several of the aminophenyloxazoles have been diazotized, using sodium nitrite and hydrochloric acid (16, 76, 78, 98) or amyl nitrite (76). The resultant diazonium compounds enter into such usual reactions as replacement by hydrogen, using hypophosphorous acid, to give 21-34 per cent yields of the phenyloxazole (16, 98); decomposition on boiling with water to give a compound that is "almost certainly" a phenol (78); and coupling with diethyl- and dimethyl-anilines to give orange products that turn crimson in acid, with resorcinol, with β -naphthol to give crimson products, and with R salt to give fluorescent, carmine products (76, 78). The diazonium compounds from 2-(*o*-aminophenyl)-5-phenyloxazole and the corre-

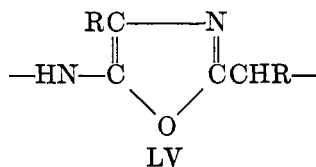
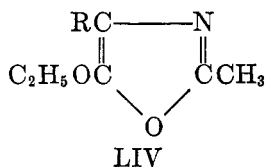
sponding *m*-amino derivative are quite stable to heat. The ortho compound decomposes at 128°C., while the meta compound melts at 153°C. and decomposes at a slightly higher temperature.

3. Ethoxyoxazoles

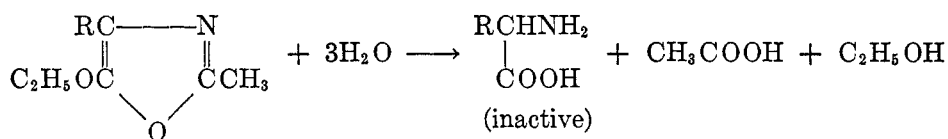
The 5-ethoxyoxazoles have been examined by Karrer and his collaborators (40, 41, 63, 64, 87) in connection with the possible occurrence of an oxazole ring in proteins. This subject has already been mentioned, and the corresponding arrangement of the atoms in the oxazoles and the polypeptides has already been pointed out (II, III, IV). On the basis of this similarity a polymeric chain containing oxazole units (LII) can be constructed from the polypeptides (L) by a simple dehydration.



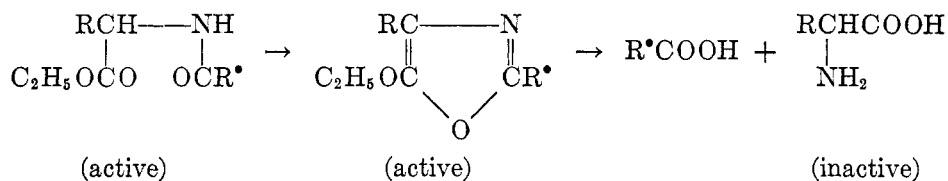
This suggests the possibility that oxazole rings may actually occur as units in the protein molecule, and this possibility is supported by the fact that oxazoles can be obtained by the acetylation of proteins (120, 121, 122, 123). Karrer proposed to obtain information about a similar monomeric oxazole to see if the properties of such an oxazole would be consistent with its occurrence in the proteins and polypeptides and selected the 5-alkoxyoxazoles (LIV), whose preparation from acylamino acid esters has been described previously, for study. The 5-alkoxyoxazoles are sufficiently closely related to the 5-alkaminooxazole unit (LV) which occurs in LII to indicate with reasonable certainty that the latter unit could not function as the unit of a polymer having the properties of the proteins.



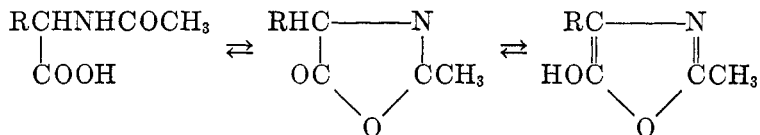
This certainty arises from the fact that the 5-alkoxyoxazole molecule on hydrolysis gives optically inactive amino acids, while optically active amino acids are obtained on the hydrolysis of the proteins. This result is to be anticipated, since in the 5-alkoxyoxazoles (LIV) the precursor of the optically active carbon atom of the amino acid is the symmetrical No. 4 carbon atom of the ring, and hydrolysis should produce a *dl* pair and not one isomer to the exclusion of the other.



Only by an asymmetric synthesis could optically active amino acids be formed during the hydrolysis, and such a possibility has been excluded in the case where the R group in the 2-position, whose source is the acid radical of the acylamino group, is optically active. With such compounds the hydrolysis products are an inactive amino acid and the active acid of the acyl group.



The examples studied had *d*-campholyl (40) and *d*-leucyl (64) as the optically active R* groups, and in each case an inactive amino acid was formed on hydrolysis. A similar hydrolytic behavior is to be predicted for the polymer (LII). The possibility that the polymer could be formed and stabilized as the tautomeric oxazoline imine (LIII), in which there could be an optically active carbon and from which optically active amino acids could be obtained on hydrolysis, is remote. It has been shown that acylamino acids are readily racemized under mild conditions (15, 115), and this is attributed to the formation of the oxazolone and its rapid tautomerism with the oxazole form.



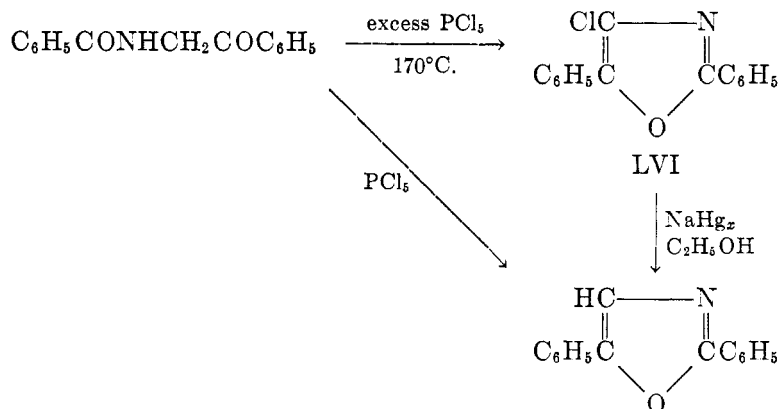
The same type of tautomerism between LII and LIII is possible and could conceivably destroy the optical activity of LIII rapidly and under mild conditions.

There is much conjecture in connection with this problem and more questions are raised than can be satisfactorily answered. As will probably have been noticed by now, it is not functionally possible to derive from α -amino acids a polymer which has a 5-alkoxyoxazole unit. The difunctionality is destroyed in

the cyclization. As a result the experimental investigations with such a type of compound cannot provide more than a supposition as to the chemical nature of the unit of a polymer such as LII or of the polymer itself. Certainly this problem is one which merits further investigation.

4. Chloroöxazoles

Although there is little positive evidence for the existence of any chloro-substituted oxazoles, some products have been isolated and characterized which are apparently chloroöxazoles. Gabriel (35) isolated a compound, $C_{15}H_{10}ClNO$, by treating benzoylaminoacetophenone with excess phosphorus pentachloride at $170^{\circ}C$. instead of the 2,5-diphenyloxazole, $C_{15}H_{11}NO$, obtained at lower temperatures with less phosphorus pentachloride. When the chloro compound is treated with sodium amalgam and ethanol, 2,5-diphenyloxazole is formed.



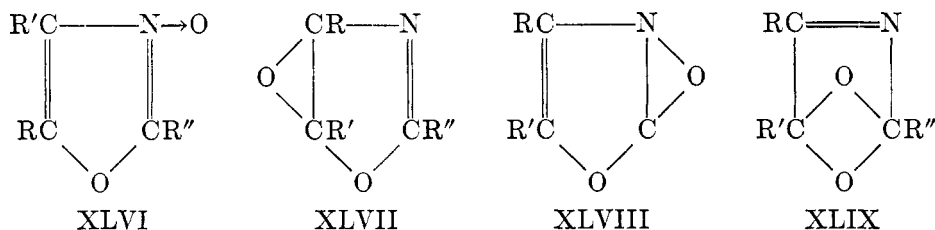
A somewhat similar reaction is observed in the formation of chlorinated pyridines by the action of phosphorus pentachloride on pyridine (106), and the inference is that the compound is 2,5-diphenyl-4-chloroöxazole (LVI). Two compounds obtained by Schwanert (105) from hippuric acid and phosphorus pentachloride and analyzing as C_9H_6ClNO and $C_9H_5Cl_2NO$ are possibly chloro derivatives of 2-phenyloxazole. Rügheimer (100) also obtained a compound $C_9H_5Cl_2NO$ by a similar process, but none of these compounds has been thoroughly characterized.

5. Oxidoöxazoles

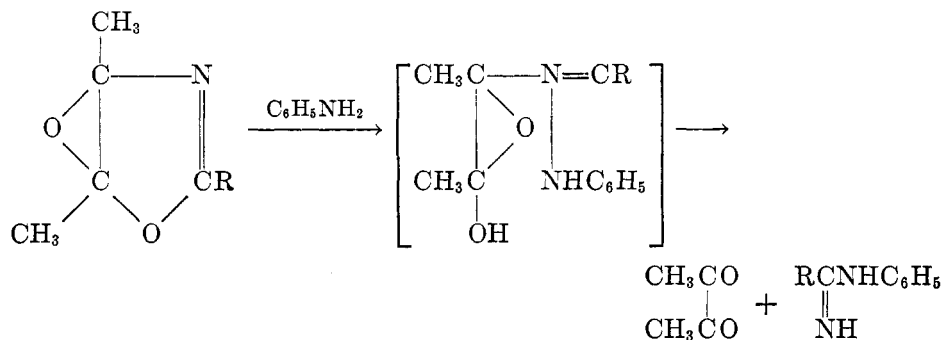
The oxidoöxazoles, whose preparation and reduction to oxazoles have been discussed, form hydrates and hydrochlorides. They are characterized by the ease with which they oxidize potassium iodide to iodine and with which they are reduced to oxazoles. They are unstable to light and cannot be stored for any length of time without decomposition. They do not react with NH_2OH or with semicarbazide, indicating the absence of carbonyl groups, but do react with phenyl isocyanate and with aniline. With phenyl isocyanate carbon dioxide is evolved and the oxidizing power of the oxidoöxazole is lost, a result which indi-

cates the replacement of the loosely held oxygen by an *N*-phenyl group. In the reaction with aniline an unstable intermediate is formed, and this can be decomposed by dilute oxalic acid to biacetyl and *N*-phenylbenzamidine oxalate (23, 24).

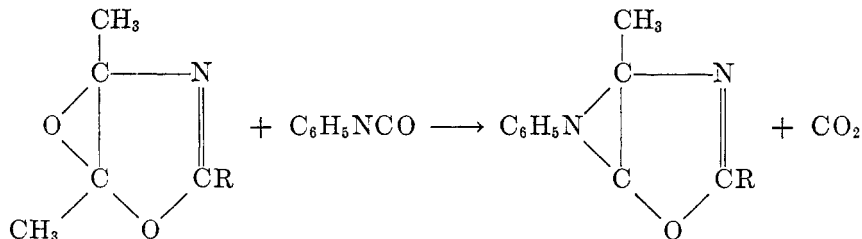
The analysis indicates that the oxidooxazole formed from the monoxime of a diketone RCOCOR and an aldehyde RCHO has the molecular formula $R_3C_3NO_2$. The ease with which reduction to the oxazole R_3C_3NO takes place indicates the presence of an oxazole ring, and the difficulty in assigning a structure to the oxidooxazoles lies in determining the proper position for the second oxygen. Several possible structures have been suggested previously (XLVI, XLVII, XLVIII, XLIX).



There is little or no experimental data to support a preference for any of these formulae. The reaction with aniline has been written using the epoxy formula (XLVII)

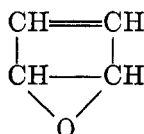


as has also the reaction with phenyl isocyanate.



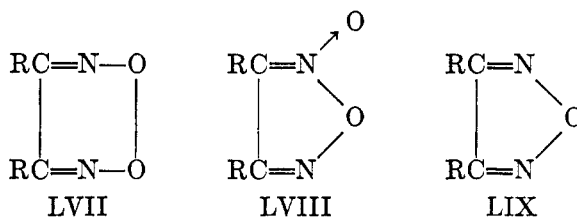
The former reaction is perhaps best explained at present by the XLVII type formula, but the latter reaction and oxidizing properties are probably satisfactorily explained by any of the possible formulae.

There are certain properties of the oxidoöxazoles which are similar to those of the tertiary amine oxides. Both form hydrates, are readily reduced to the free amines by nascent hydrogen, decompose on standing, and form salts with acids. These similarities suggest the plausibility of the oxide-type formula (XLVI) and receive support in the fact that an oxide can be prepared from pyridine by the action of perbenzoic acid (82). It may also be noticed with reference to the epoxy formulae that the ethylene oxide formula



has been suggested as a possible form for the furan ring in order to account for its 1,4-addition reactions such as that with maleic anhydride (38).

The problem of the structure of the oxidoöxazoles is similar to the problem of the structure of the furoxanes (LVIII). In the furoxanes, which can be prepared by oxidation of the dioximes of α,β -diketones and can be reduced to the furazanes (LIX) (6), the second oxygen has also been assigned various positions, including that in such epoxy and oxide structures as LVII and LVIII. The evidence for the various forms has been summarized up to 1936 (10).



No attempt will be made here to summarize the extensive and conflicting work that is being carried out in studying the structure of the furoxanes. The similarity of the structural problems is cited here, since it is possible that information concerning the structure of the two series of compounds can be correlated as it becomes available.

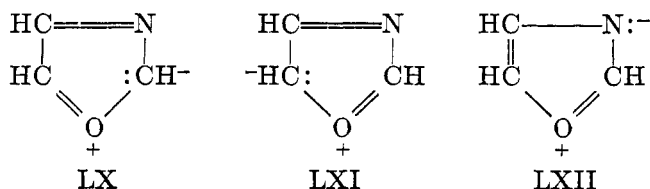
IV. STRUCTURE

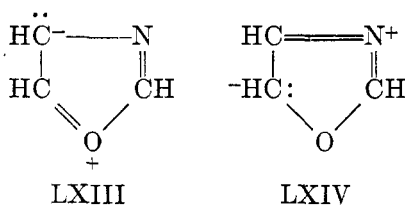
The chemical data thus far considered indicate that the oxazoles are unsaturated cyclic compounds having a formula similar to that originally proposed by Japp (I, IV). The analyses demonstrate the low hydrogen content and the formation by loss of water in appropriate cases, both of which can be explained on the basis of such an unsaturated, cyclic compound. The preparation of triphenyloxazole by five different methods and of 2,5-diphenyloxazole by three different methods substantiates the fundamental correctness of the formula. In fact, there would probably be no question as to the suitability of this formula unless it was already known that in similar cyclic compounds a diminished unsaturation or "aromaticity" is observed. If the oxazoles could be shown to have aromatic properties then the same problem, in explaining the decreased

reactivity of the double bonds, would arise as is encountered with benzene, pyridine, furan, and many other types and one might postulate a stabilization due to resonance. Before postulating the presence of such resonance, however, the aromaticity of the oxazoles must be established, and with this in mind the properties of the oxazoles will be compared with those properties usually associated with aromaticity.

The essential aromatic properties are the peculiarly diminished unsaturation and the tendency toward formation and preservation of type; these have been carefully discussed recently (28, 93). The tendency toward formation of the oxazoles may be seen in the several synthetic methods which in some cases, as with the aldehyde and cyanohydrin reaction, probably involve unique rearrangements. The reactions of the oxazoles showing their tendency toward preservation of type are associated with their diminished unsaturation. This diminished unsaturation of aromatic compounds is commonly observed as a tendency to undergo substitution rather than addition reactions, but there are no known reports of successful substitution reactions with oxazoles. Such substitution reactions as halogenation and the Friedel-Crafts reaction have apparently not been attempted with the oxazoles. The inconclusive data on the sulfonation of phenyloxazoles have been mentioned. A resistance toward substitution has been noted in the formation of nitrophenyloxazoles instead of nitrooxazoles in the nitration reactions, and it has been mentioned that this indicates a behavior similar to that of the pyridines, which are nitrated only under very vigorous conditions, (80) rather to that of the furans, which are nitrated or sulfonated under very mild conditions (39, 51).

Although evidence of oxazole aromaticity as measured by occurrence of substitution reactions is not available, the resistance of the oxazoles toward addition of hydrogen is an example of a type of diminished unsaturation observed with other aromatic compounds. This one fact is sufficient to create a presumption of aromaticity and when coupled with the formal analogies with the furans and the pyridines the conclusion that aromatic properties are present is probably sufficiently well founded to support recent classifications (110) of the oxazoles as aromatic compounds. More complete data would certainly aid in stating the exact position of the oxazoles as aromatic compounds and in supporting the necessity for the postulation of possible resonance forms. Two types of physical measurements support such conclusions. The presence of a dipole moment, even though small, indicates the presence of polar molecules such as would be expected if resonance occurred (89). The molecular refractivity data show in some cases the same type of optical depression that is observed with other types of heterocyclic compounds that are considered to be aromatic (5). Some of the possible types of polar forms which could be present as resonance forms are:





The first four of these are similar to the four polar forms of furan which have been proposed (117a) and the last is similar to the polar formula suggested for pyrrole (109).

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