THE CHEMISTRY OF 4,5-DIHYDRO-5-OXO-1,3-OXAZOLES

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Abstract - 4,5-Dihydro-5-oxo-1,3-oxazoles are important class of heterocycles and interest in their chemistry continues unabated because of their usefulness as synthons. In this review an attempt has been made to present the chemistry of this class in an integrated form and in proper perspective under the following headings:

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1. INTRODUCTION

Of the several oxo derivatives of dihydro-1,3-oxazoles (1) - (5), the chemistry of 4,5-dihydro-5-oxo-1,3-oxazoles (1), more commonly known as 2-oxazolin-5-ones or simply 5(4H)-oxazolones, have engaged the maximum attention of chemists because of the synthetic importance of this class of compounds.

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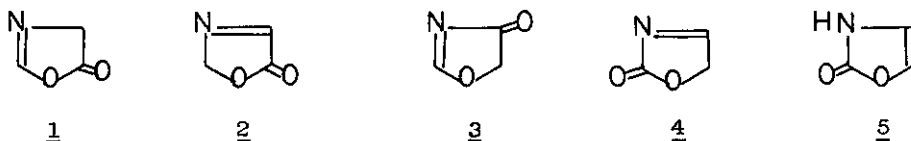
Historically, Plöchl was the first chemist to discover the product obtained by the interaction of hippuric acid and benzaldehyde in acetic anhydride, but it was Erlenmeyer who rationalised the structure as 7, extended the reaction to other aldehydes, and ushered in this class of compounds to prominence, christening them as "azlactones"[1]. Since then the reaction is known as Plöchl-Erlenmeyer or simply as Erlenmeyer azlactone synthesis.

$$PhCONH-CH_2COOH + PhCHO \xrightarrow[-H_2O]{Ac_2O/AcONa}$$

| 6 | 7 |
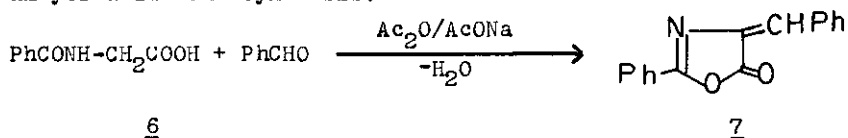
It is noteworthy that penicillin was originally assigned the now discarded thiazolidine-oxazolone structure and as such many new facts regarding 5-oxazolones came to light in connection with the penicillin-program during the second world war[2]. As a result of vigorous and sustained research, vast material accumulated over the years, as is evidenced by the number of reviews published from time to time[1-6], and there is no abatement in its proliferation. In this article an
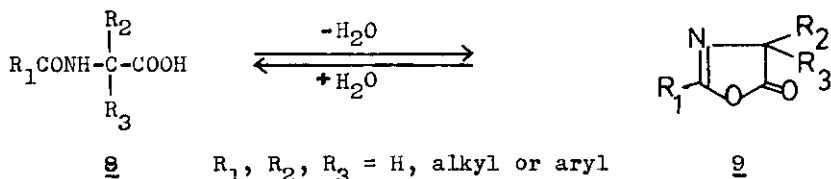
attempt has been made to present the subject in an integrated form and in its proper perspective.

2. SYNTHESES OF 4,5-DIHYDRO-5-OXO-1,3-OXAZOLES

Though simple heating of α-acyl(aroyl)amino acids has been used to construct 2-oxazolin-5-ones, this method is not of practical importance. Generally, some cyclising agent is used for this purpose. Besides, there are some other routes to these systems.

2.1. Cyclisation of α-Acyl(Aroyl)amino Acids by Organic Reagents:

Heating with acid anhydrides, particularly acetic anhydride, continues to be the most common practice for cyclodehydration of α-acyl(aroyl)amino acids[3]. Erlenmeyer was unable to obtain $\underline{9}$ because of the instability of such compounds. Later workers have been successful in isolating some of these 2-oxazolin-5-ones in moderate or good yields in fairly pure state. Depending upon stability, the

$$R_1CONH-\overset{\overset{\textstyle R_2}{|}}{\underset{\underset{\textstyle R_3}{|}}{C}}-COOH \quad \underset{+H_2O}{\overset{-H_2O}{\rightleftharpoons}} \quad$$

$$\underline{8} \qquad R_1, R_2, R_3 = H, \text{ alkyl or aryl} \qquad \underline{9}$$

product can be separated by decomposition of the unreacted acetic anhydride with an excess of water[7,8] or by removal of the excess reagent and acetic acid under reduced pressure[9], and finally by distillation of the residue or recrystallisation from suitable solvent. Fused sodium acetate has been usually applied as a condensing agent but its use is not an imperative one.

Use of acid chlorides, such as acetyl chloride in dioxan, and chloroacetyl chloride in the presence of potassium carbonate is known in the literature[2]. Similarly benzyl[2] and ethyl[10] chloroformates and a tertiary base were used to prepare 2-oxazolin-5-ones, but these reagents have not found favour for unknown reason. Recently, it was shown that α-acyl(aroyl)amino acids undergo smooth cyclisation to the corresponding 2-oxazolin-5-one with ethyl chloroformate in the presence of triethylamine in benzene[11], and this procedure is quite convenient for generating these heterocycles in situ.

N,N'-Dicyclohexyl carbodiimide[12], which is extensively used in the peptide synthesis, found application in the preparation of several 2-oxazolin-5-ones.

Recently, a method of obtaining chemically and optically pure 4-substituted 2-oxazolin-5-ones by the use of soluble N-ethyl, N'-(γ-dimethylamino propyl) carbodiimide hydrochloride[13] was developed.

Benzophenone dichloride, which was reported to be useful for anhydride formation, was employed for the preparation[2] of 2-oxazolin-5-one, but its applicability is not very clear.

Recently, hippuric acid was found to give 9 (R₁= Ph; R₂= R₃= H) on treatment with 1-methyl-2-halopyridinium salts[14]. The scope of this reagent for the preparation of 2-oxazolin-5-ones remains to be explored.

2.2. Cyclisation of α-Acyl(Aroyl)amino Acids by Inorganic Reagents:

There are several inorganic compounds which have been reported to be useful for the preparation of 2-oxazolin-5-ones. For example, phosphoryl chloride in pyridine, thionyl chloride, phosphorus tribromide, phosphorus pentachloride and phosgene may be mentioned[2]. α-Acyl(aroyl)amino acids, on reaction with acid halide-forming reagents, give 5-oxazolonium hydrohalides[2,3] and not the corresponding acid halides which were earlier erroneously considered existant. Recently, benzyloxycarbonyl glycine was cyclised with some of these reagents, and it was found that 9 (R₁= PhCH₂O; R₂= R₃= H) is difficultly obtained when phosgene, thionyl chloride or phosphorus oxychloride and triethylamine in tetrahydrofuran[15,16] are used at -20°C. The result was better with phosphorus pentachloride, by using 10% excess and maintaining low temperature for 25 min[16].

Phenylthioacetyl glycine[3] and thiobenzoyl glycine[2,3] (10) with silver oxide in ether undergo cyclisation to 9 (R₁= PhCH₂ or Ph; R₂= R₃= H) apparently by attack of the carboxylate ion on the thioamide group aided by silver oxide in removal of the sulphur atom[2,3].

$$R_1CSNH-CH_2COOH \xrightarrow[-H_2S]{Ag_2O/ether}$$

10   9
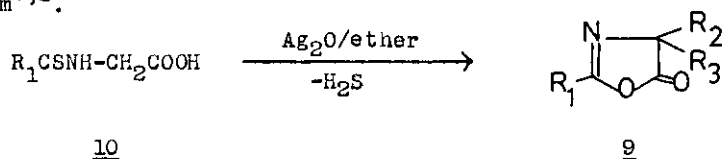
Recently, use of polyphosphoric acid (PPA) for the stereospecific synthesis of 4-arylidene-2-phenyl-2-oxazolin-5-ones (13) was reported (Scheme 1)[17]. The reaction has been claimed to produce 12 as an intermediate which subsequently

cyclises to 13. It is not clear why hippuric acid itself does not undergo cycli-
sation in the first place in presence of PPA which is a powerful dehydrating
agent. This point needs further clarification. Also, the authentic (Z)-izomer
changes to the corresponding (E)-isomer[17] under the influence of PPA, and it is
quite likely that PPA acts as an isomerising agent besides bringing about cyclo-
dehydration of 6 and concomitant condensation with 11.

Scheme 1

6   11   R₁= Me or H; R₂= aryl 12   13
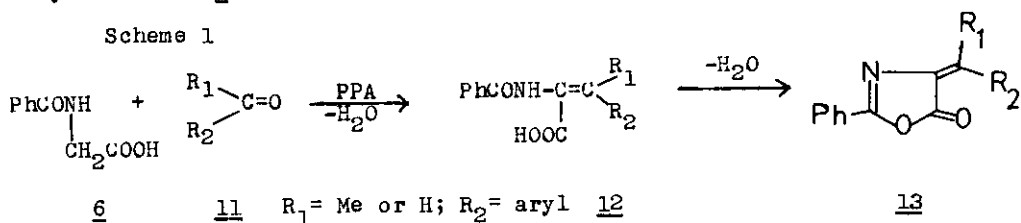
## 2.3. From Other Heterocycles:

Conversion of some heterocycles into 2-oxazolin-5-ones are known in the
literature, but it is not a straightforward reaction and it involves several
steps. Therefore its practical utility is limited.

4-Arylidene-2-thiohydantoin (14), on heating with two to four fold excess
of aroyl chlorides in pyridine gave 17 in high yields, possibly through 15
(Scheme 2)[18,19].

Scheme 2

14   15   17
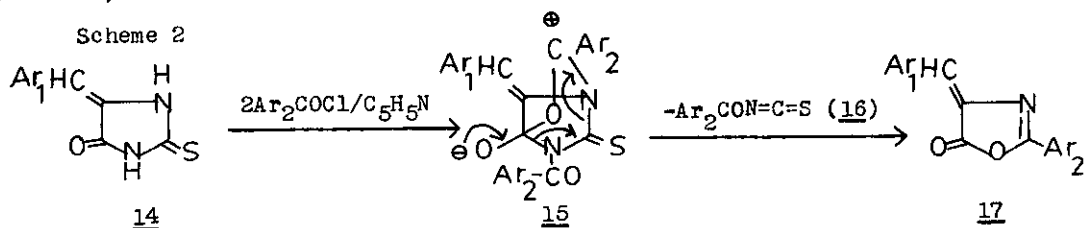
The isothiazolidin-5-one 1,1-dioxide (18), on treatment with acetic
anhydride in pyridine, afforded the (E)-isomer of 2-oxazolin-5-one (21)[20] through
the intermediates shown in Scheme 3.

Scheme 3

18   19   20

21
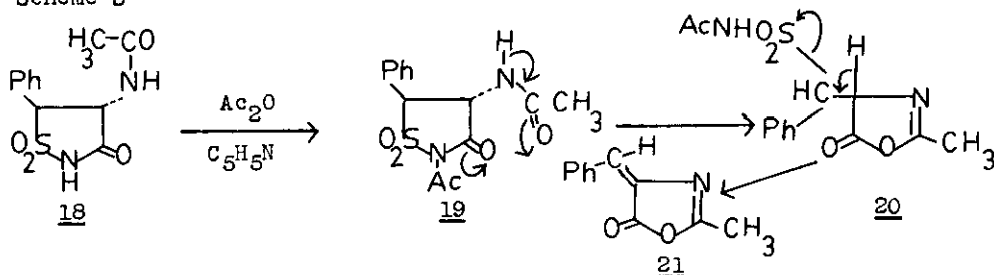
A number of 3-aroylamino-2-azetidinones (22) have been reported to give 25 (R$_1$ and R$_2$ = aryl), via acid catalysed 1,2-bond cleavage (Scheme 4)[21]. This method is not of practical utility because the route is circuitous and a mixture of products is obtained resulting into poor yield of the resultant 2-oxazolin-5-ones (25). Somewhat similar transformation is encountered when anhydropenicillin (26) is treated with mercury (II) acetate in benzene[22]. The oxidative
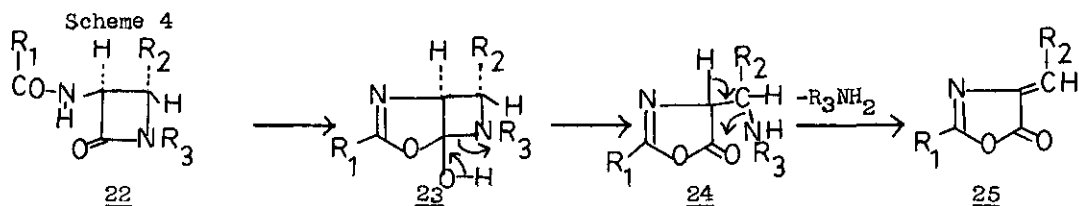
Scheme 4

rearrangement of 26 to 27 obviously envisages an intermediate formed by cleavage of the 4,7-bond. The compound 27 exists as tautomers (Scheme 5).
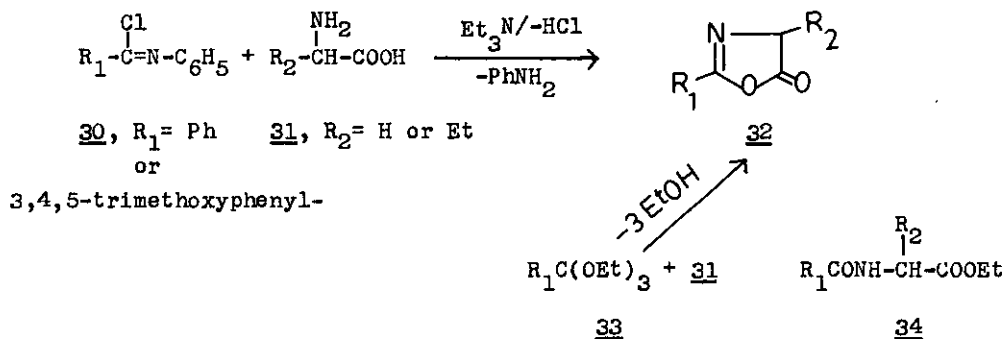
Scheme 5
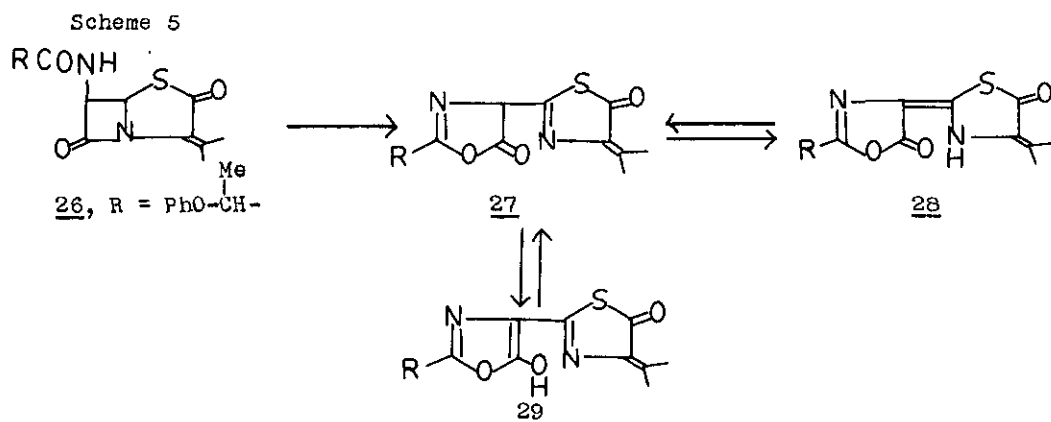
Recently, a derivative of 2-oxazolin-5-one was implicated in the conversion of penicillin V sulphoxide by extra cellular enzyme[23]. Also, the rearrangement of methyl benzyl penicillinate to methyl benzyl penicillenate is noteworthy in this connection[24].

2.4. Miscellaneous Syntheses:

Glycine and DL-∝-aminobutyric acid react with N-phenyl-arylimidoyl chlorides (30) in benzene, containing triethylamine, to give 32 in moderate yields (Scheme 6)[25,26].
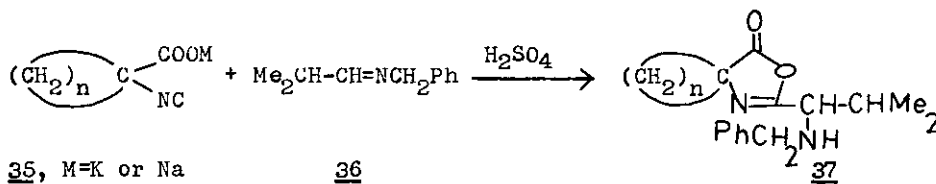
A similar reaction of amino acids, such as alanine, valine, isovaline and methionine, with orthoacetates in dimethyl acetamide leads to the formation of a
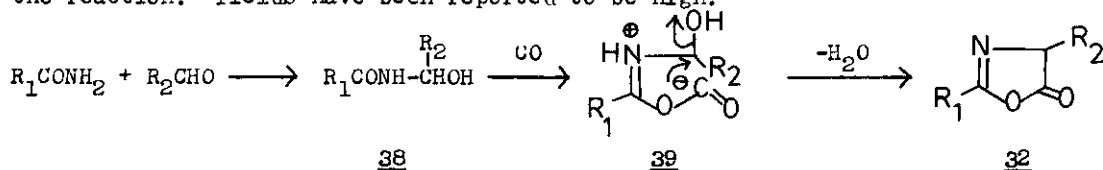
Scheme 6

$$R_1-\overset{Cl}{\underset{}{C}}=N-C_6H_5 + R_2-\overset{NH_2}{\underset{}{C}}H-COOH \xrightarrow[-PhNH_2]{Et_3N/-HCl}$$

$\underline{30}$, R_1= Ph $\underline{31}$, R_2= H or Et

or

3,4,5-trimethoxyphenyl-

$$\xrightarrow{-3EtOH}$$

$R_1C(OEt)_3 + \underline{31}$ $R_1CONH-\overset{R_2}{\underset{}{C}}H-COOEt$

$\underline{33}$ $\underline{34}$

mixture of α-acylamino acid esters ($\underline{34}$) and 2-oxazolin-5-ones ($\underline{32}$), the former apparently being formed by alcoholysis of $\underline{32}$ during the reaction[27]. Yields are low.

     Potassium or sodium salt of α-isocyanocarboxylic acid ($\underline{35}$), on neutralisation with a mineral acid in the presence of an aldimine and immediate shaking the mixture with a water-immiscible solvent, gives the spiro compound $\underline{37}$[28]. It should be mentioned that addition of the aldimine after neutralisation did not afford the 2-oxazolin-5-one ($\underline{37}$). This method cannot be considered as a general one.

$$(CH_2)_n C \overset{COOM}{\underset{NC}{<}} + Me_2CH-CH=NCH_2Ph \xrightarrow{H_2SO_4}$$

$\underline{35}$, M=K or Na $\underline{36}$ $\underline{37}$

     Recently, a number of 2-oxazolin-5-ones were prepared by dehydration of primary amides, aldehydes and carbon monoxide in the presence of group VIII metals or their compounds[29]. Apparently, the reaction proceeds through the intermediate $\underline{38}$, and this is supported by the fact that the amidol ($\underline{38}$) itself can be used in the reaction. Yields have been reported to be high.

$$R_1CONH_2 + R_2CHO \longrightarrow R_1CONH-\overset{R_2}{\underset{}{C}}HOH \xrightarrow{CO} \xrightarrow{-H_2O}$$

$\underline{38}$ $\underline{39}$ $\underline{32}$

     Nitrones, such as $\underline{40}$ and $\underline{43}$ give spirooxazolones ($\underline{42}$ and $\underline{44}$) respectively on reaction with ketenes (Scheme 7)[30-32]. This method is not a very general one and different products are obtained from other nitrones.

Scheme 7

42, R$_1$= Ph, Me, 1-Pr etc.
R$_2$= Ph or Me

43   44
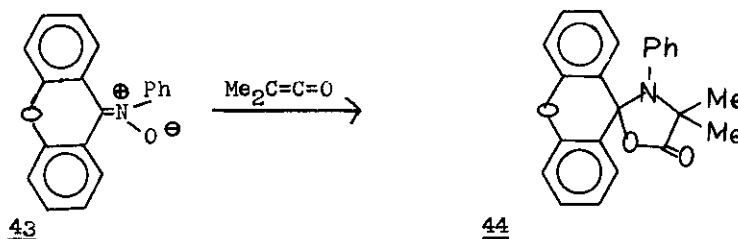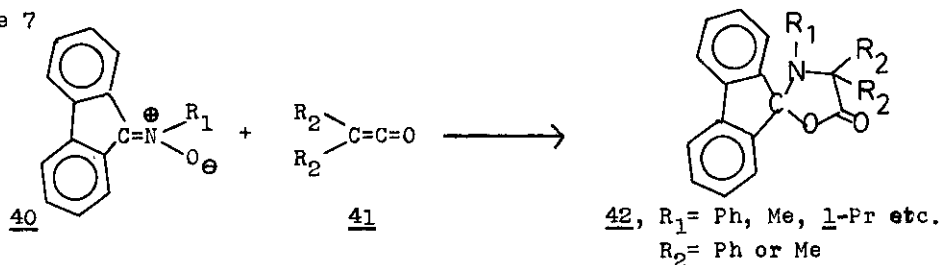
Conversions of some 5-allyloxyoxazoles into 2-oxazolin-5-ones are also
known in the literature. Thus, N-aroylleucine 3-methyl-2-butenyl esters (45) were
cyclised with triphenyl phosphine/hexachloroethane/triethylamine in acetonitrile
at 0° to 46 which changed to 47 via Claisen rearrangement (Scheme 8)[33].

Scheme 8

45, R=aryl   46   47
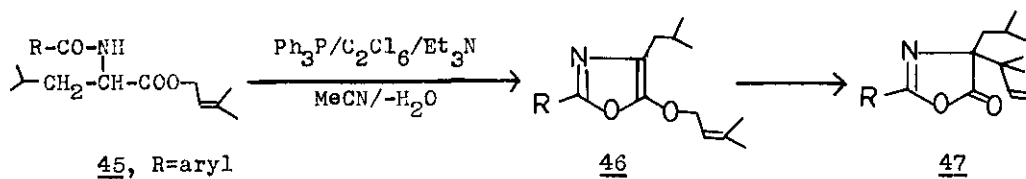
3. REACTIONS OF 4,5-DIHYDRO-5-OXO-1,3-OXAZOLES

2-Oxazolin-5-ones give diverse products with different reagents and the
reaction may involve retention or collapse of the heterocycle, 4-alkylidene(aryli-
dene) derivatives being more stable than the corresponding saturated compounds.
Also, the C-2 substituent affects the stability and reactivity of the ring. It
should be mentioned that in many reactions cleavage of the ring occurs as a result
of secondary process. In others, the reaction is initiated by opening of the ring.

3.1. Reactions without Cleavage of the Ring:

3.1.1. Formation of Oxazolonium Salts

As already mentioned, α-acylamino acids with acid halide-forming reagents
give products which have been confirmed as oxazolonium hydrohalides. Boyd and

co-workers have found that cyclisation of α-acylamino acids with acetic anhydride
in the presence of perchloric acid affords stable 5-oxazolonium perchlorates from
which free bases can be separated[34]. These perchlorates have been found to be
useful in obtaining the unstable isomers of 4-arylidene-2-oxazolin-5-ones.

3.1.2. Tautomerism and Related Reactions

If C-4 hydrogen is available, 2-oxazolin-5-ones behave as mesoionic
compounds[35-38] and can exist as one of the several tautomers, such as 32, 48-50.
This has been profitably utilised in carrying out C-4 substitution with alkyl,
benzyl and allyl halides in the presence of ethyl diisopropylamine in dipolar
aprotic solvents[39-41]. Also, C-4 hydrogen can be substituted by halogen. Thus,
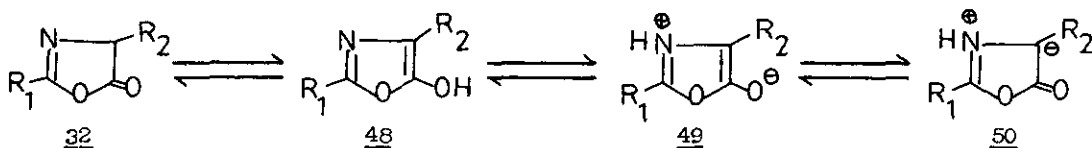
51 on treatment with sulphuryl chloride afforded 52 which reacts with benzyl
thiol to give 4-S-benzylthio compound (53a). Similar reaction of 52 with thio-
acetic acid, followed by hydrolysis, afforded the stable 2-benzamido-2-mercapto-
propanoic acid (54) which on oxidation with iron (III) chloride in ether dimerised
(Scheme 9)[42]. It is noteworthy that 51 nor its anion reacted cleanly with
α-toluenesulphenyl chloride and similar was the case with sulphur monochloride.
However, the anion reacted with S-benzyl p-toluenethiosulphonate.

Scheme 9
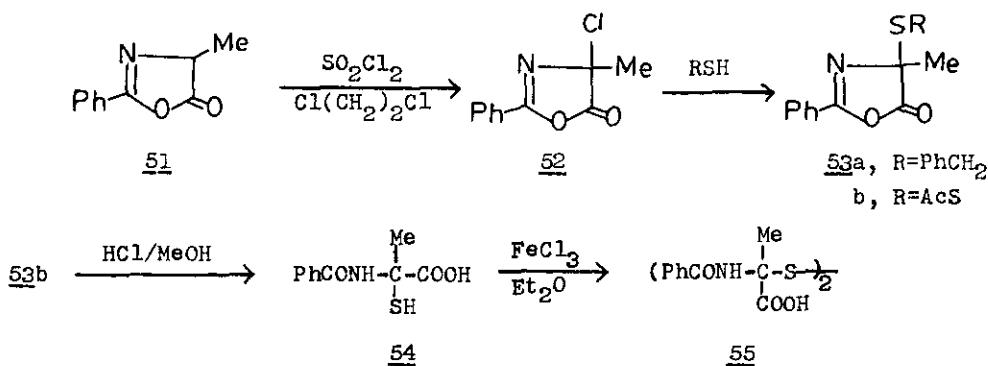
Recently, 5-hydroxyoxazole (48) was trapped with cyclopropylcarbonyl[43],
carbethoxycarbonyl[44], and trimethylsilyl[9,45] groups. The Dakin-West reaction[44]
obviously involves migration of O-acyl groups to C-4, especially when aided by
pyridine derivatives. 4-Dialkylaminopyridines are quite useful for such

transacylation and recently they were reviewed[46].

4-Acyl-2-oxazolin-5-ones ($\underline{57}$, R_2=H) can exist as tautomers ($\underline{57}$) and ($\underline{58}$) and studies on 2-phenyl-4-(1-heteroalkylidene)-2-oxazolin-5-ones revealed that they exist in the form having exocyclic double bond[47].

$$\underline{56} \quad\longrightarrow\quad \underline{57} \quad\overset{R_2=H}{\rightleftharpoons}\quad \underline{58}$$
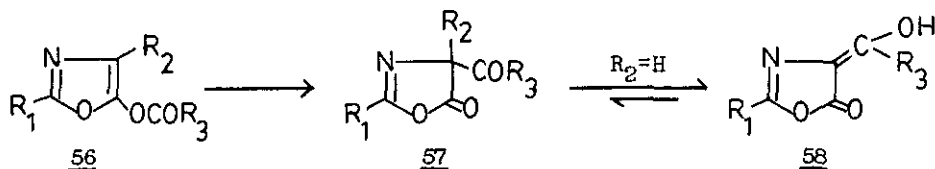
### 3.1.3. Formation of the 4-C=C Bond

As already mentioned, Erlenmeyer synthesis involves condensation of the C-4 active methylene group with aldehydes and ketones[3]. Aromatic aldehydes give better result. Aliphatic carbonyl compounds are generally taken in excess to get better yields[8]. When aldehydes are used as reactants a condensing agent is not necessary, but for ketones some metal salts, such as sodium acetate and lead acetate[48,49], are required. Recently, tin (IV) chloride has been recommended for reactants like acetals, ketals and ketones[9]. Also, solid drying agent, such as molecular seive, has been used for the formation of 4-C=C bond under mild condition[50]. Application of polyphosphoric acid[17] for the preparation of ($\underline{E}$)-isomers has already been mentioned. A complex of dimethyl formamide and sulphur trioxide was reported to be useful for the preparation of 4-arylidene-2-phenyl-2-oxazolin-5-ones[51].

Erlenmeyer azlactone synthesis and its modified versions are useful routes to $\propto$-amino acids and other important synthetic intermediates, and in this connection diverse aldehydes and ketones have been inserted at the 4-position. This reaction has been extended to carotenoids[52], carbohydrates[53], pyrilium, silapyrilium and thiopyrilium salts[54] and other heterocycles[55]. Recently, it has been used for construction of tetracycline[56]. Also, azlactone synthesis with pyrene-3-aldehyde was employed for the detection of acylglycines by paper chromatography[57]. It is noteworthy that several bis-2-oxazolin-5-ones ($\underline{59}$)-($\underline{61}$) have been synthesised and used for dying polyester fibres[58-60].
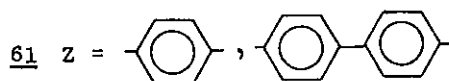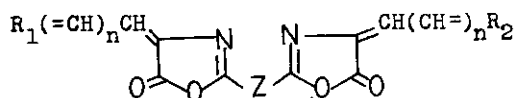
In a recent modification of Erlenmeyer synthesis, imines derived from aniline[11,61], benzyl-[62,63] and n-butylamines[63] were used and it was found that the
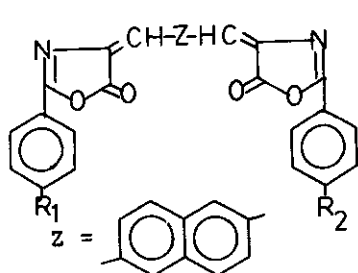
59a, $R_1 = R_2 = H, Cl, Me$ or OMe
 b, $R_1 = H$ or OMe; $R_2 = Me$ or OMe

60, R=heterocycle

61 Z =
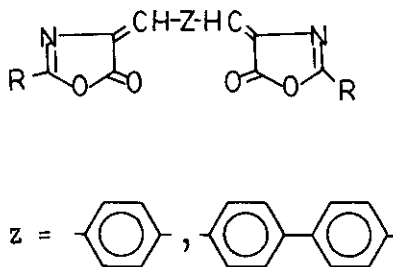
n = 0,1; R_1, R_2=heterocycle

reaction proceeds fast. No condensing agent is required in this case and ketimines reacted directly unlike the corresponding ketones[11]. The reaction however failed when ketimines derived from benzophenone and benzil were used as reactants[63]. This is apparently due to steric factor. It should be mentioned that the products obtained by this modification are mostly the (Z)-isomers[11]. Erlenmeyer synthesis and its modified versions envisage formation of an unstable adduct 64 which immediately undergoes β-elimination to give 65, and formation of β-lactone (66, Y=O), β-lactam (66, Y=RN) or their derivative was not observed in any of the cases (Scheme 10).

Scheme 10

62

63, Y=O, PhN, PhCH$_2$ and n-Bu

64

65, R_1=alkyl, aryl
    R_2=alkyl, aryl
    R_3=H or alkyl

66
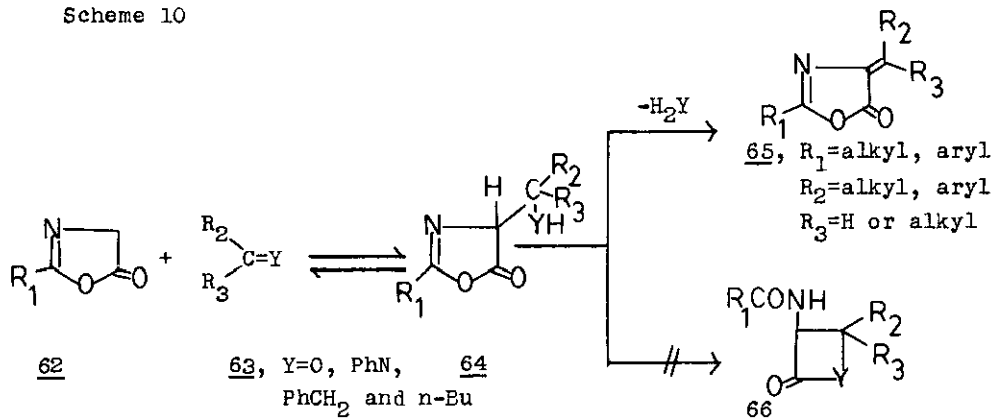
Some similar reaction occurred with enamine[64] and amidines[2,3]. When imines were used as reactants partial aminolysis of 65 occurred due to cleavage of the 1,5-bond by the resultant amine[11].

2-Phenyl-2-oxazolin-5-one (67) reacted with 2-alkyl-2-thiazolines (68) in pyridine to give 73 in 75% yield. When benzene was used as a solvent, compounds 73 and 71 were obtained in 6.5% and 8.5% yields respectively[65]. Obviously the reaction involves nucleophilic addition to thiazoline, followed by cleavage of the 1,2- and 2,3-bonds of the resultant thiazolidine and concomitant thiolysis and aminolysis, respectively, of another molecule of 67 (Scheme 11). Earlier, similar nucleophilic attack on 77 was reported to give methyl phenyl penillonate (78A) or methyl phenyl penicillenate (78B)[66] depending on whether the reaction is carried out in neutral medium or in pyridine. Recently, an oxazolone inter-mediate has been implicated in the rearrangement of methyl benzyl penicillinate to methyl benzyl penillonate[24]. When lactim ethers (74)[65,67,68] were used as reactants 75 were obtained some of which cleaves[65] depending on the starting material (Scheme 12).

Scheme 11
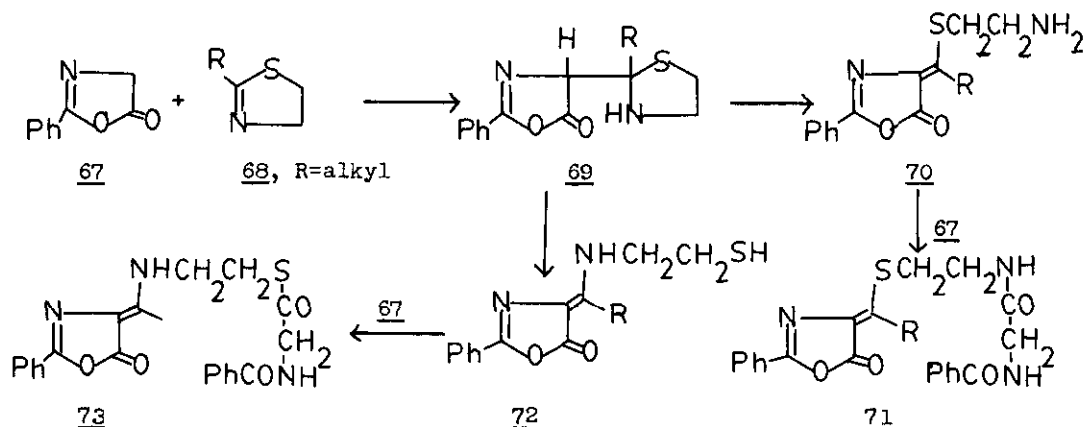
It should be mentioned that similar addition to some other compounds containing carbon-nitrogen double bond, such as oximes, O-acyl oximes and hydrazones was unsuccessful[69].

4-Heteromethylene-2-oxazolin-5-ones (81) are also important in this connection. For example, 4-alkoxymethylene-2-oxazolin-5-ones (80), which can be prepared by condensing orthoformic esters (79) with 62, easily give the corres-

Scheme 12
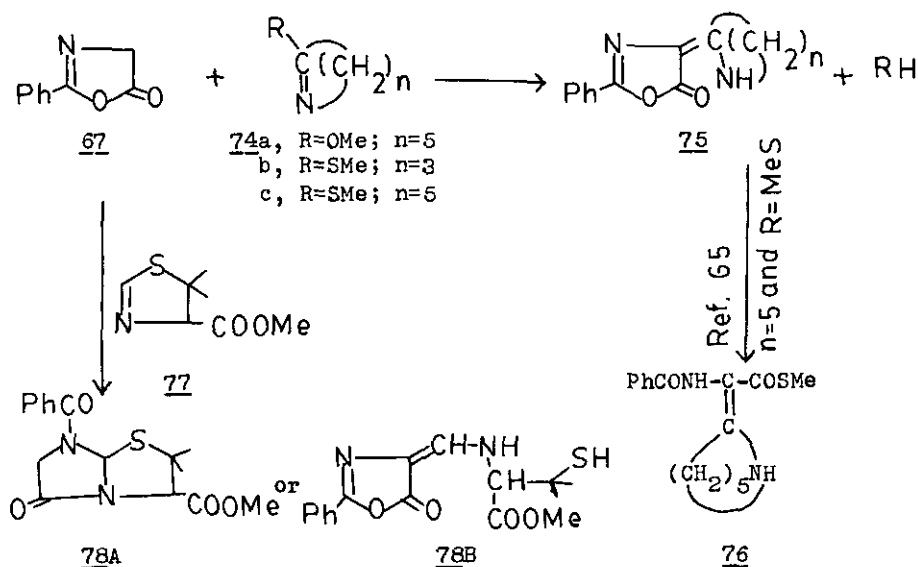
ponding 4-hydroxy compounds 81a or aminomethylene derivatives 81c under mild conditions[2-4]. The hydroxy compounds behave like acid and can exist as tautomers which have already been mentioned. It is noteworthy that 81a can be converted into reactive chloro compounds 81b which are useful for the synthesis of 2-oxazolin-5-ones with 4-C=C bond in cases where the aldehyde is not readily available[70]. Recently, 4-ethoxymethylene-2-phenyl-2-oxazolin-5-one (80, R_1= Ph; R_2= EtO) was employed for obtaining several 4-pentenylidene derivatives serving as intermediates for ibotenic acid[71]. It should be mentioned in this connection that some of the aminoalkylidene derivatives 81c resist substitution as well as ring cleavage.
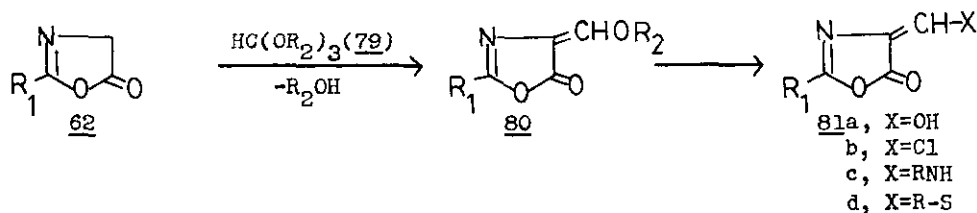

Synthesis of several 4-alkylidene(arylidene)-2-oxazolin-5-ones have been accomplished by Bergman's method[2,3,72]. Recently, 4-dichloromethylene-2-aryl-2-oxazolin-5-one (83) was obtained in good yields from 82 by cyanation, hydrolysis and cyclisation with phosphorus pentachloride[73]. As already mentioned, the chloro group in compounds like 83 is quite reactive and has been replaced by several

secondary amines, but the reaction with primary amines cleaves the ring.
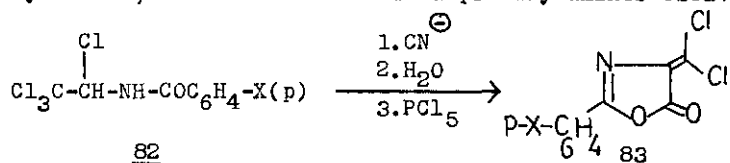
Recently, 4-benzylidene-2-benzyloxy-2-oxazolin-5-one (85) was prepared by bromination of 84 and subsequent dehydrobromination of the resultant bromo compound[16]. Alternatively, it was prepared in fair yield by treating benzyloxy-carbonyl threo-β-phenyl serine (86) with phosphorus pentachloride at low temperature, but starting from erythro-isomer lower yield was obtained, though in both the cases a single isomer was found. It is noteworthy that diethyl azodicarboxylate failed to convert 84 into the corresponding 4-benzylidene derivative 85, though the same reagent satisfactorily dehydrogenated 87 to 7 (Scheme 13)[16].

Scheme 13
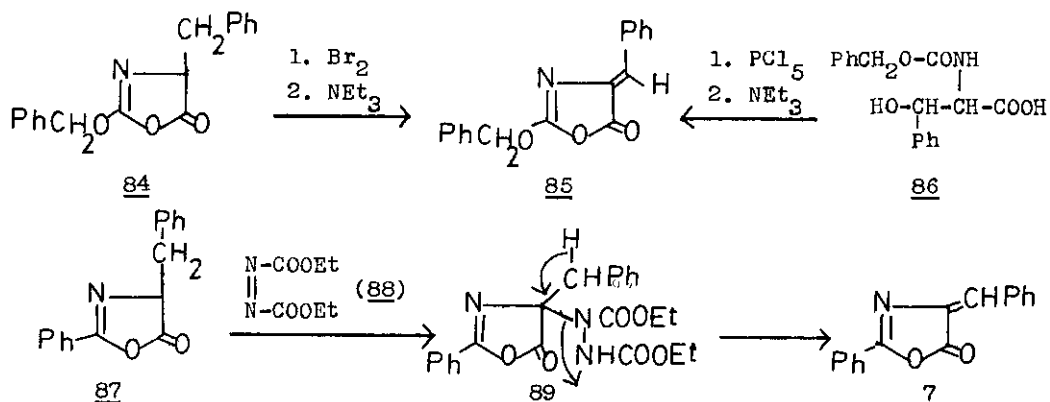
4-Alkylidene(arylidene)-2-oxazolin-5-ones can exist as two geometrical isomers and their formation depends on the reaction conditions. Generally, the (Z)-isomer is more stable than the corresponding (E)-isomer which is thermolabile. These two isomers are interconvertible, and recently their stereochemistry was reviewed[74]. Also, their characterisation by ^{13}C-NMR[75], Raman[76], and fluorescence spectra[55] has been reported.

3.1.4. Reactions involving the 4-C=C Bond

A common reaction involving 4-C=C bond is reduction and it is extensively practised in the synthesis of amino acids. Besides catalytic hydrogenation, hydroiodic acid and red phosphorus are also used[3,77]. It should be emphasised

that the 2-oxazolin-5-ones are generally cleaved before reduction because this gives better result. Some of the methods for preparation of amino acids have been discussed in another section.

Addition of diazomethane can lead to different products. For example, 90 gave the spiro compound 91 obviously by the insertion of the carbene moiety or by elimination of nitrogen from the resultant pyrazoline adduct. Some of these compounds have been degradated, and an attempt to obtain cyclopropylphenylalanine (92) led to the formation of styrylglycine (93) in low yield (Scheme 14)[78]. It is noteworthy that β, γ-unsaturated amino acids have stimulated interest in recent years[79].

Scheme 14
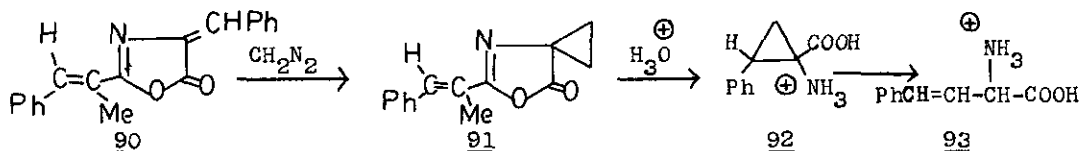
Recently, alkylation of 94 with lithium phenylthio-n-butylcuprate was effected and the resultant compound was converted into a useful aldehyde (96) by ring cleavage and oxidation[40].
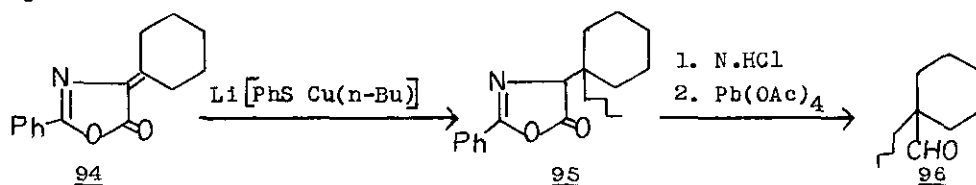
2-Oxazolin-5-ones with 4-C=C-bond are α, β-unsaturated carbonyl compounds, but their potentiality as participants in the Michael reaction does not seem to have been thoroughly exploited, though addition of some mercaptans or bifunctional reactants attacking simultaneously the olefinic bond and carbonyl group is known in the literature[3,6].

3.1.5. Michael Addition

2-Oxazolin-5-ones containing a C-4 hydrogen atom give Michael adducts[80-82] with suitable reagents, addition taking place at positions 4 and 2. A number of unsaturated compounds, such as acyl or aroyl acetylenes, acetylene sulphone[80], acrylonitrile, methyl esters and nitriles of fumaric and maleic acids, acraldehyde

and methyl vinyl ketone, have been used as reactants. These adducts are quite useful intermediates. For example, the 2-oxazolin-5-one (32) added to acetylenes (97) from which γ-diketones (101) were obtained (Scheme 15)[81]. Recently, Michael addition followed by suitable manipulation afforded β, γ-unsaturated amino acids[80].

Scheme 15

| 32 | 97, R_3=Ph, Me$_2$CH, Me | 98 | 99 |

100

$R_2CO-CH_2-CH_2-CO-R_3$ + R_1COOH + NH_3

101, R_2= Me, Me$_2$CH, $\overset{Me}{\underset{Et}{\diagdown}}$CH, PhCH$_2$,

MeS-CH$_2$CH$_2$, PhCONH(CH$_2$)$_4$, MeOOC-CH$_2$,
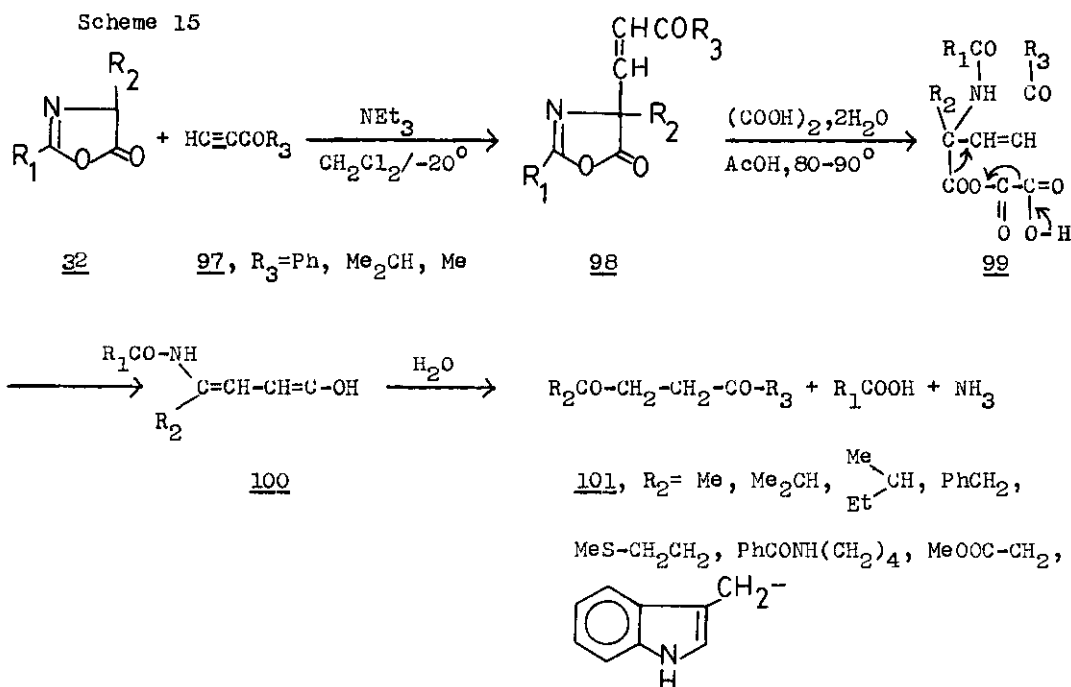
4-Methyl-2-phenyl-2-oxazolin-5-one (51) reacts with benzylideneaniline to give an unstable adduct 103 which decomposes on boiling with aqueous ethanol to anilide (107) and benzaldehyde[83]. Earlier, this reaction was reported to give the β-lactam (104)[84,85]. Recently, 104 has been synthesised by an unambiguous route and found to be quite stable[86]. It has been suggested[83] that the anilide (107) is produced as a result of dissociation of 103 to 105 or 106 and concomitant generation of aniline (Scheme 16), which ultimately leads to the aminolysis of 51.

3.1.6. Mannich Reaction

2-Oxazolin-5-ones carrying at least a C-4 hydrogen atom are capable of producing Mannich bases. The reaction occurs with simultaneous cleavange of the 1,5-bond[87].

Scheme 16
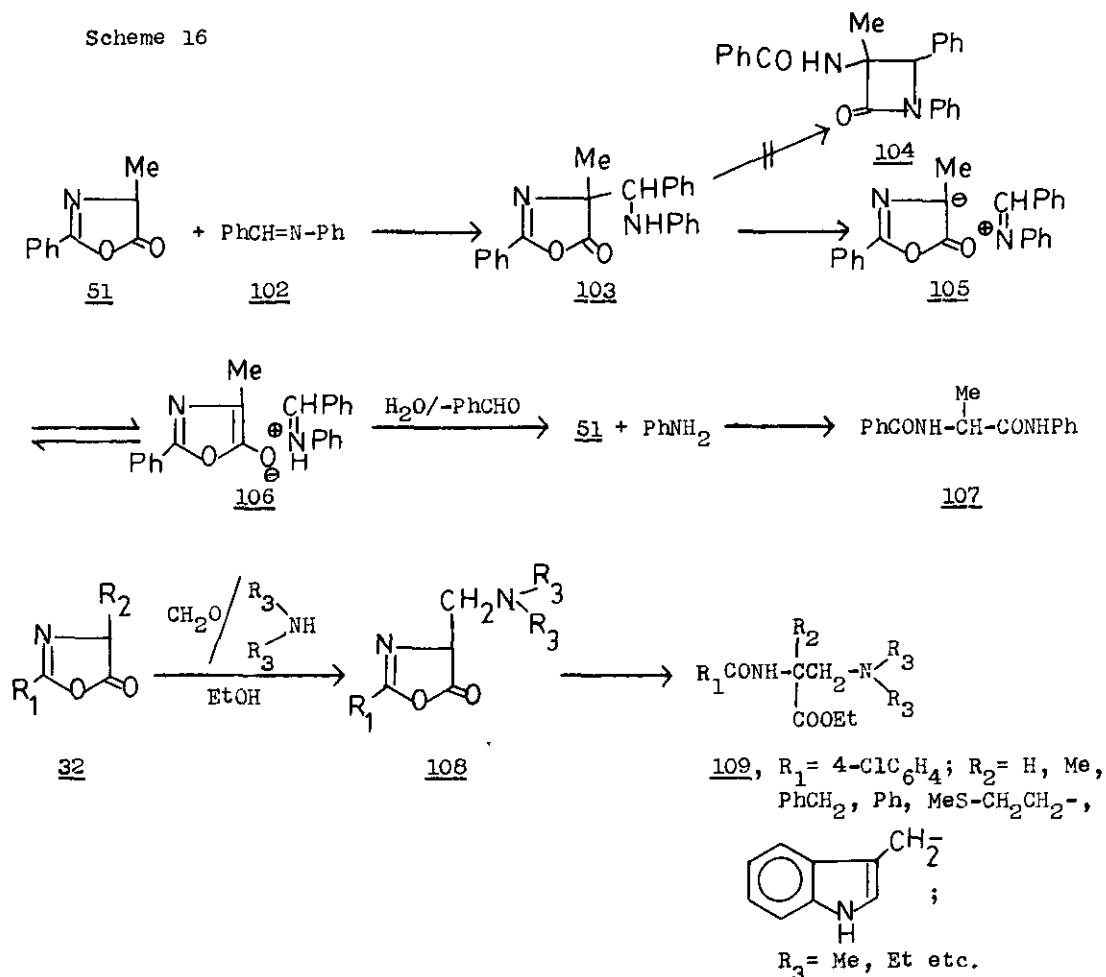
3.1.7. Cycloadditions

Those reactions in which cycloaddition does not cleave the heterocycle in the first step are discussed here. Since many of the 2-oxazolin-5-ones behave as mesoionic compounds, their reactions with a suitable addendum proceed in a typical 1,3-dipolar fashion. Recently, mesoionic compounds have been reviewed[88].

Acetylenes and reactive alkenes react with 2-oxazolin-5-ones to give pyrroles[35-37,89] and pyrrolines[90] respectively. Similar reaction of acetylenes with 2-oxazolin-4-ones leads to the formation of furan derivatives[91], as a result of cycloaddition and concomitant decarboxylation. On using dimethyl fumarate, methyl acrylate as dipolarophiles, 2-oxazolin-5-ones give pyrrolines[90], but recently, α-chloroacrylonitrile (110) was reported to give pyrrole isomers on reaction with 2-oxazolin-5-ones (32) (Scheme 17)[38]. It should be mentioned that

4-unsubstituted 2-oxazolin-5-ones failed to react.

Scheme 17

R_1=H,Me,$\underline{i}$-Bu,Ph $\quad$ R_2= Me, $\underline{i}$-Bu,Ph
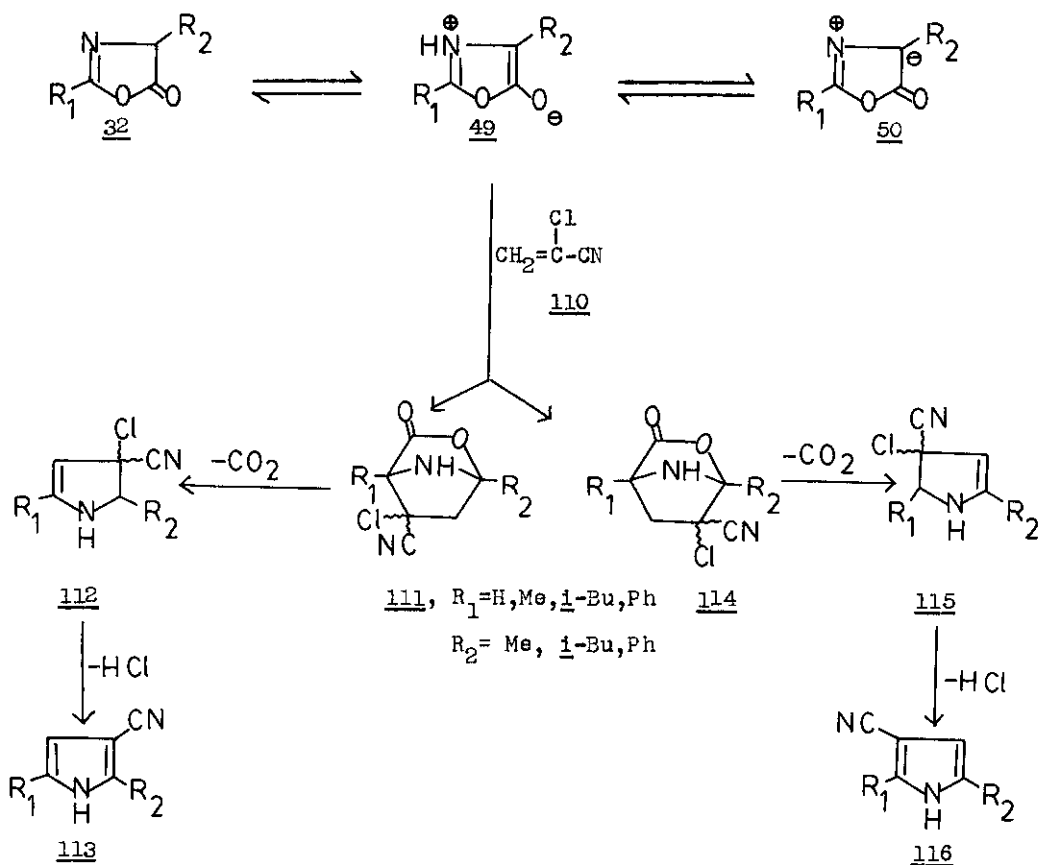
Recently, 5-trimethylsilyloxy derivatives were subjected to Diels-Alder reaction with several dienophiles and the resultant adducts were converted into vitamin B_6 derivatives (Scheme 18)[45].

Scheme 18
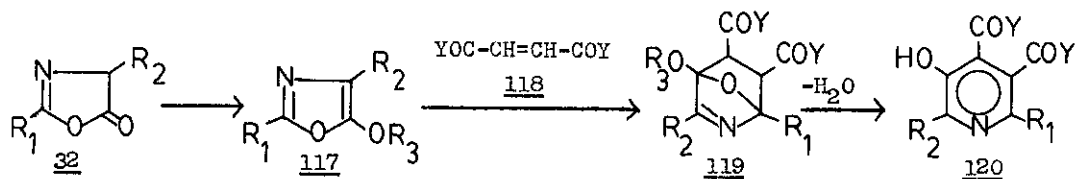
R_1= Me, Ph, etc; R_2= H, PhCH$_2$, Me$_3$CH, etc; R_3= Me$_3$Si; Y = OMe or Y,Y = $>$N-Ph

3.1.8. Oxidative Coupling

2-Phenyl-2-oxazolin-5-one ($\underline{32}$, R_1= Ph; R_2= PhCH$_2$ or $\underline{i}$-Bu) undergoes

oxidative coupling[2,3] on treatment with mercury (II) acetate in dioxan. Recently, sensitised photooxygenation of 2,4-diphenyl-2-oxazolin-5-one (32, R_1= R_2= Ph) was reported to give 121, besides other degradative products[92]. Solid-phase photolysis[93] of 122 leads via asymmetric dimerisation and hydrogen abstraction to dimers 123 and 124 as main products (Scheme 19).

Scheme 19

32   121, R_1= Ph; R_2= Ph, $PhCH_2$ or $\underline{t}$-Bu

122, Ar = 4-Cl-C_6H_4-   123   124

It is noteworthy that bis-oxazolones are of several types depending on the links of the individual units which can be through C-2 as well as C-4 atoms. Also, two heterocycle-moieties may be connected to one another through the olefinic bond[4]. Generally, their synthesis is carried out by conventional method starting from suitable materials. Oxidative coupling involving C-2 atom does not seem to have been reported.
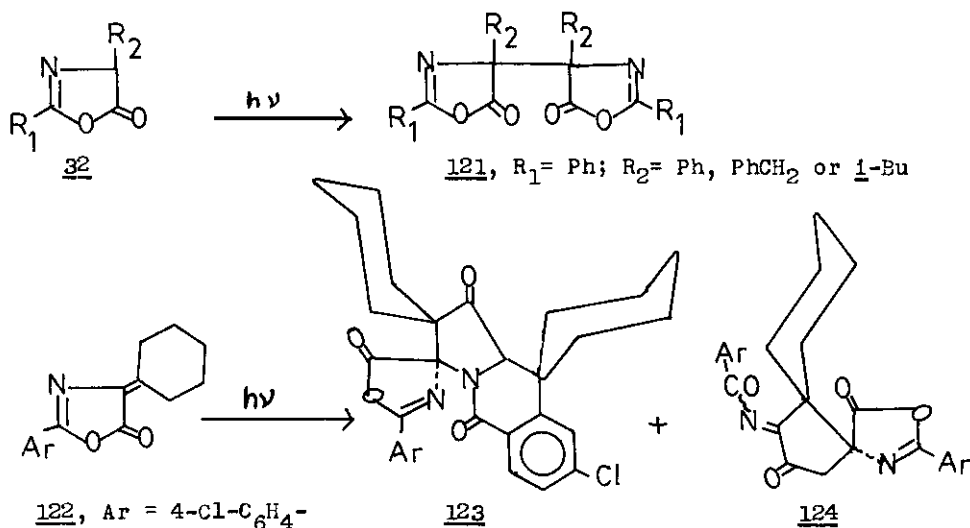
3.2. Reactions Involving Cleavage of the Heterocycle:

2-Oxazolin-5-ones can undergo cleavage at the 1,2- as well as 1,5-bonds. The course of the reaction depends on several factors. Also, stability of the ring is influenced by the substituents, and as already stated the 4-alkylidene-(arylidene) derivatives are more stable than the corresponding saturated compounds.

3.2.1. Cleavage of the 1,2-Bond

Cases of the 1,2-bond cleavage in 2-oxazolin-5-ones are rather limited. For example, hydrazoic acid with 25 (R_1= Me; R_2= Ph) afforded the tetrazole

carboxylic acid ($\underline{126}$, R_1= Me; R_2= Ph) via cleavage of the 1,2-bond and subsequent

cyclisation of the corresponding imidazide ($\underline{125}$)[94]. Yields are excellent and

there is no evidence of any side-product. Similar opening occurs with its

saturated derivative. The reaction of $\underline{25}$ becomes very slow when R_1 is a phenyl

group, where as in the reaction of 4-benzylidene 2-benzyloxy-2-oxazolin-5-one

($\underline{25}$, R_1= $PhCH_2O$; R_2= Ph) cleavage of the 1,5-bond predominates[16].
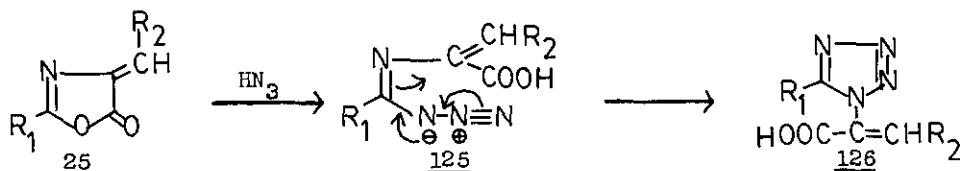
With the aid of labelled water and mass spectrometry acidic hydrolysis of

2-oxazolin-5-ones was shown to undergo cleavage of the 1,2-bond[95]. Acid

catalysed ring cleavage has also been investigated by employing acetic acid[96].

There are some other reactions in which cleavage of the 1,2-bond has been

reported[2,3].

3.2.2. Cleavage of the 1,5-Bond

The general reaction of 2-oxazolin-5-ones involving cleavage of the
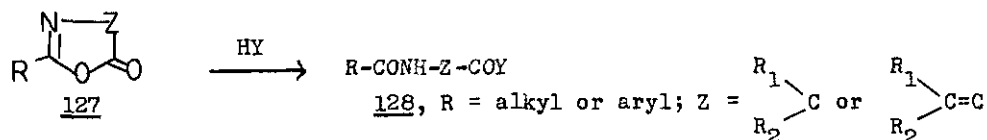
1,5-bond may be represented as follows.

The reactant YH may be water, alcohols, thiols, phenols, ammonia, primary and

secondary amines, hydroxylamine, hydrazines[2-6], phosphate anion[97] and also

enzymes[6]. The reaction is governed by several factors, such as nature of the

substituent, temperature, catalyst and the type of reactants. In general,

4-alkylidene(arylidene)-2-oxazolin-5-ones are more stable than the corresponding

saturated compounds, and many of them are recrystallised from neutral alcohols.

The carbonyl group can react with Grignard reagents[4,98-100] and can also

participate in Friedel-Crafts reactions[4,101]. Similarly, treatment with sodium

borohydride[102] or lithium aluminium hydride in a suitable solvent, such as

tetrahydrofuran, results in reductive cleavage[3].

Scheme 20

129   130

25

YNH$_2$

R$_2$CO-HN-C=CHR$_2$
      |
    Y-HNCO

131

-H$_2$O

Ref. 108-112

132, R$_1$=alkyl or aryl; R$_2$=aryl
    Y=H, alkyl, aryl, or OH

R$_1$= PhCH$_2$O
Ref. 16

133, R$_2$=aryl; Y=alkyl, aryl,
    PhNH or OH

Y=NH$_2$ or PhNH
Ref. 16,113

134, R$_1$= alkyl or aryl;
    R$_2$= aryl; R$_3$= H or Ph

R$_1$= PhCH$_2$O;
Y=NH$_2$ or PhN
Ref. 16

135, R$_2$= Ph; R$_3$= H or PhN
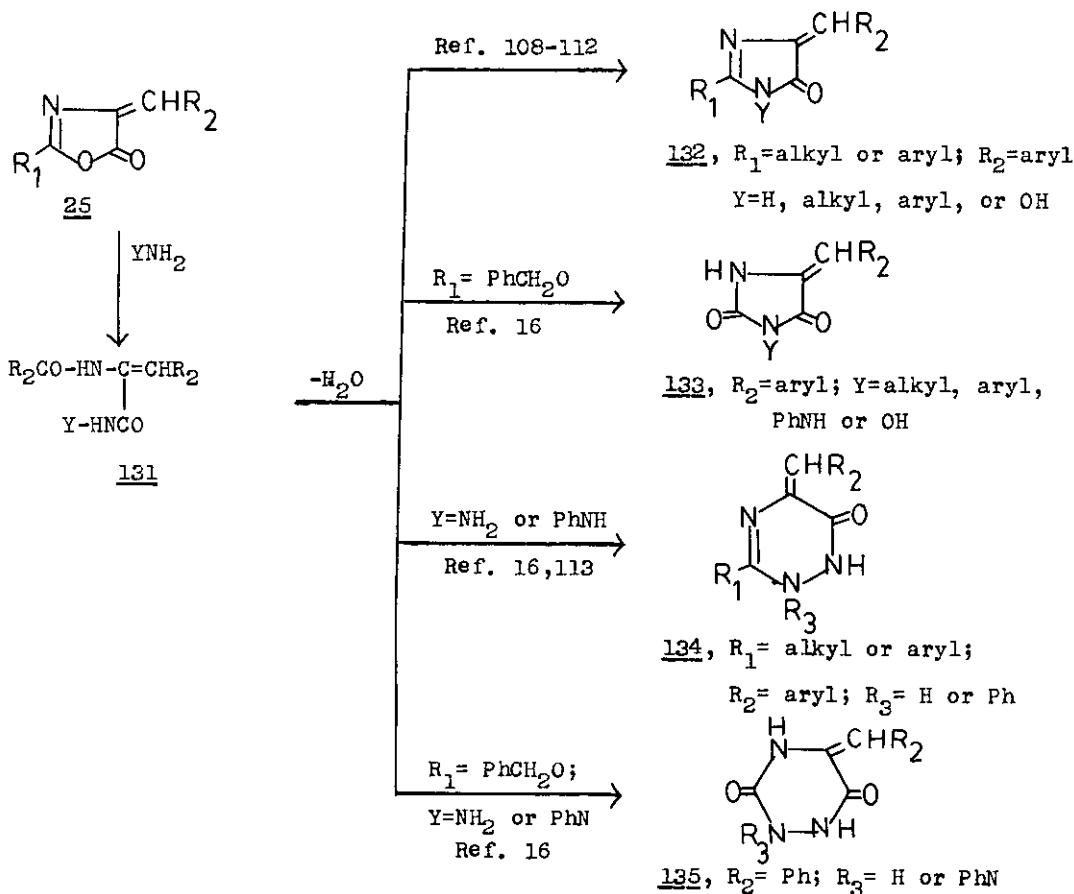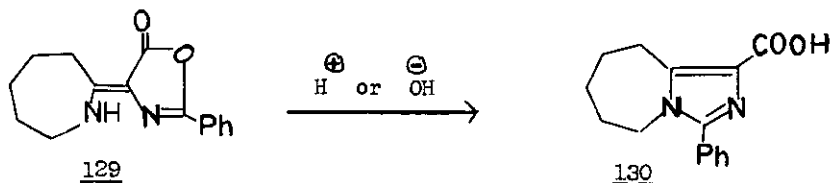
It should be emphasised that products obtained by rupture of the ring may
undergo subsequent changes, and in many cases they serve as useful intermediates.
For example, one of the most important methods of synthesis of α-amino acids is
through hydrolysis of 4-alkylidene(arylidene)-2-oxazolin-5-ones and subsequent
reduction. Often hydrolysis and reduction are carried out in one step with the
aid of hydroiodic acid and red phosphorus[3,77]. Hydrogenation of 4-alkylidene(ary-
lidene) derivative under elevated hydrogen pressures and in ammonia-ethanol, using

Raney nickel as a catalyst, leads to the formation of α-acyl(aroyl)amino acid amides in high yields[103]. Recently, alcoholysis[104,105] and aminolysis[106,107] of 2-oxazolin-5-ones were employed in polymerisation. Some of the products of the 1,5-bond cleavage are useful for construction of other rings, especially heterocycles. For example, the 2-oxazolin-5-one (129) on ring cleavage and subsequent cyclisation afforded the imidazole (130)[67]. Products of aminolysis of 4-arylidene-2-oxazolin-5-ones have been cyclised in the presence of anhydrous zinc chloride[108] or in glacial acetic acid containing catalytic amount of fused sodium acetate to the corresponding 5-imidazolones[109,110], and recently this reaction has been extended to one-flask synthesis of 4-arylidene-5-imidazolones starting from 4-unsubstituted 2-oxazolin-5-ones and Schiff bases[111]. As already indicated, the products of aminolysis of 2-oxazolin-5-ones which are amenable to cyclodehydration under the influence of an acid or a base serve as starting materials for several heterocycles (Scheme 20)[16,108-113]. It is noteworthy that 134 (R_3= H) can exist as tautomers[113].

N-Benzylthiothiocarbonylglycylamide (136), obtained by aminolysis of the corresponding 2-thiazolin-5-one, undergoes cyclisation to 137 with concomitant cleavage of the amide bond, and this reaction is potentially important for using 2-benzylthio-2-thiazolin-5-one as a protecting reagent for amines[114].
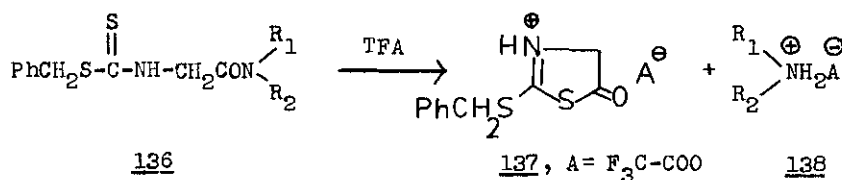
As indicated earlier, 4-alkylidene(arylidene)-2-oxazolin-5-ones may react with bifunctional compounds first at the 4-C=C bond with one of the two functionalities and subsequently undergoing cleavage of the 1,5-bond. Alternatively it could be the other way around as shown in the reaction of hydrazine hydrate with 65[115]. Recently, amidinoacetic ester was reported to give 145[116] on reaction with 65, apparently by Michael addition followed by intramolecular aminolysis (Scheme 21).

Earlier, hydroxylamine was reported to give 5-isoxazolidones (146) with 65[117]. An attempt to obtain these heterocycles by the interaction of 2-oxazolin-

Scheme 21
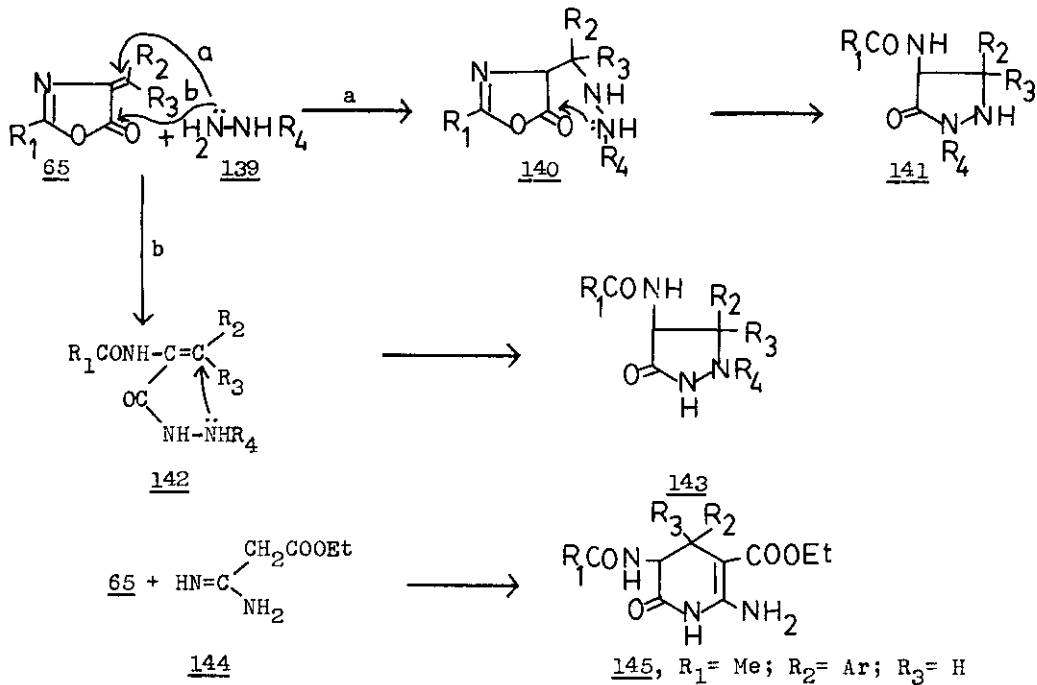
5-ones (62) and suitable oximes was unsuccessful (Scheme 22) and the reaction led
to the formation of O-acyl oximes which are potentially important as acylating
agents for primary amines[118].

Scheme 22
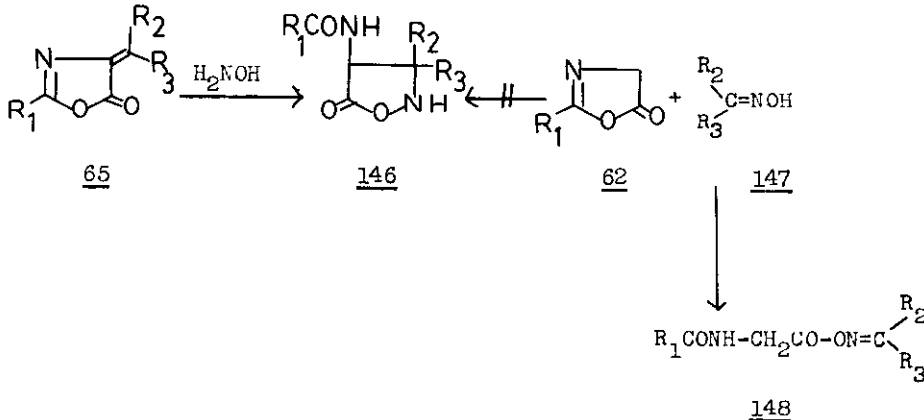
As already mentioned, hydroxamic acids are formed on aminolysis of 2-oxazolin-
5-ones with hydroxylamine. It should be emphasised that when 65 are used as
reactants various products are obtained with hydroxyl amine[119]. For example,
addition can take place across the 4-C=C-bond, and recently such adduct-forming
property has been utilised in the synthesis of α, β-diamino acids[120], which can

be alternatively prepared by manipulation of 3-substituted pyruvic acids[121].

Some 4-arylidene-2-oxazolin-5-ones, on photoradiation, undergo solvolysis or abstract hydrogen atom depending on the wave length, concentration and choice of the sensitiser. Thus, 65 (R_1= R_2= Ph; R_3= H) on irradiation in 2-propanol afforded the lactone (151) in 17% yield (Scheme 23)[122,123]. Conversion of the (Z)-4-salicylidene-2-phenyl-2-oxazolin-5-one (157) into its (E)-isomer similarly results in the formation of 3-benzamido coumarin (155, R_1= Ph)[124,125]. Rao[17] has

Scheme 23

65, R_1= R_2= Ph; R_3= H   149

150   151
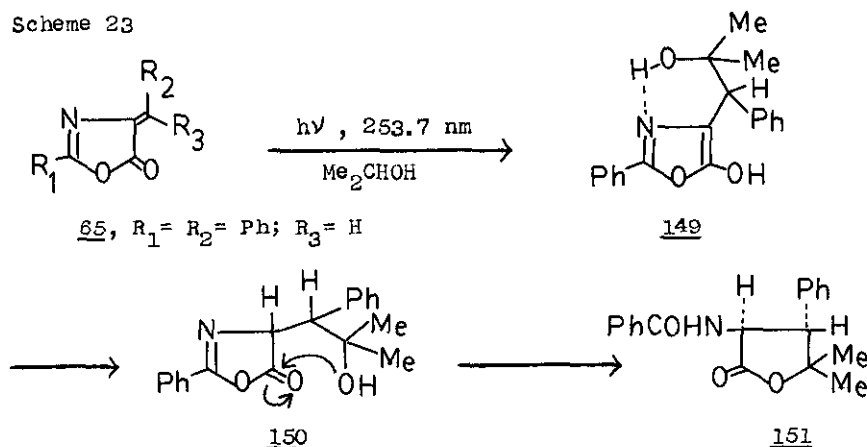
reported synthesis of the (E)-isomer 156 by condensation of hippuric acid and salicylaldehyde in the presence of PPA, but the absorption band quoted for the carbonyl group in the IR spectrum is not compatible with the oxazolone structure and it is more appropriate for the coumarin (155) which would be easily formed because of the steric disposition of the carbonyl and salicylidene groups. Recently, a number of 3-amidocoumarins have been synthesised[126] and an alternative route has been proposed (Scheme 24) which is supported by the isolation of dihydrocoumarins (154, R_2= Me, Y = PhN or O)[83].

Scheme 24

32   152, Y = PhN or O   153   154, R_1= alkyl or aryl; R_2= Me,H; Y = PhN or O

155   156   157
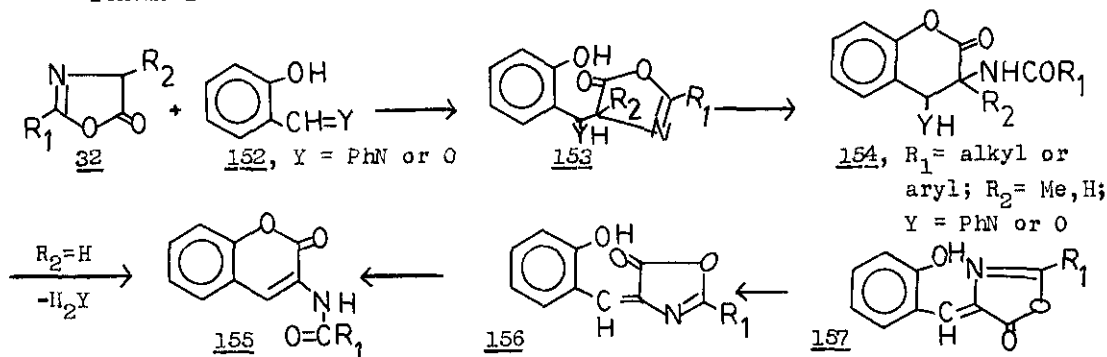
Cleavage of the 1,5-bond in 85 by diazomethane has been recently reported[16]. This behaviour is similar to that of the corresponding 2-benzylthio-2-thiazolin-5-one, and in this reaction formation of 1:1 adduct is not discernible.

85        $\xrightarrow[\text{ether}]{CH_2N_2}$ 158
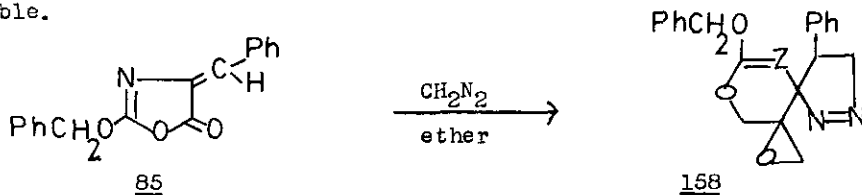
The reaction of spiro-2-oxazolin-5-one (159) with excess of diazomethane afforded the diazoketone (161) and a number of other products (Scheme 25)[127], some of which were formed as a result of progressive ring expansion.

Scheme 25
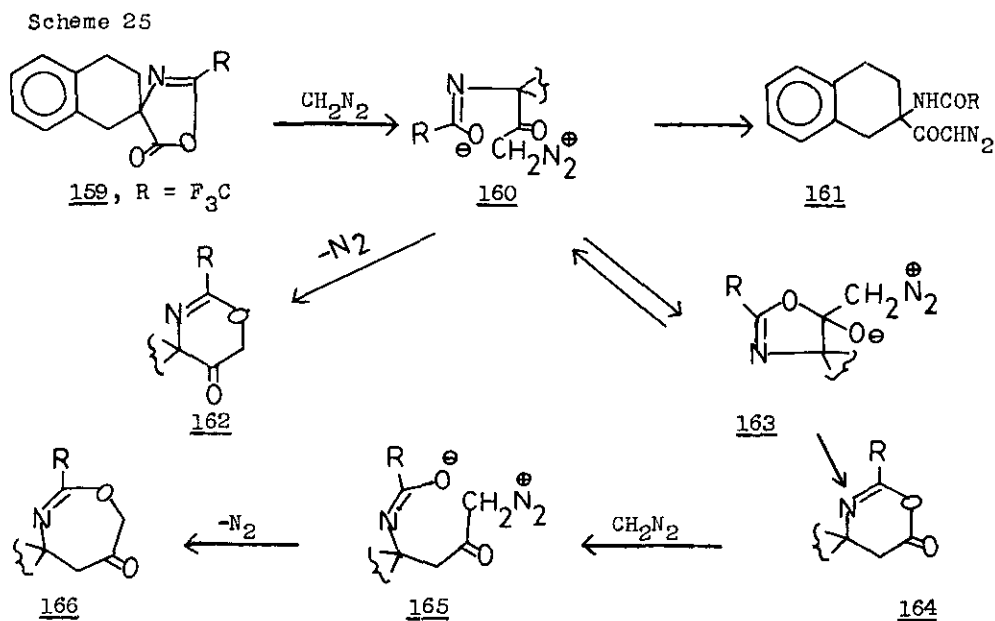
There are some reactants with which cycloadducts are formed through cleavage of the 1,5-bond. For example, some mesoionic oxazolones[128,129] added to benzylideneaniline and other imines to give β-lactams[128]. Also, formation of a δ-lactam by the reaction of 4-methyl-2-phenyl-2-oxazolin-5-one with cinnamylideneaniline is known in the literature[130]. It is noteworthy that the perchlorate salt 167 led to the formation of imidazolone (168)[64] on reaction with 102.
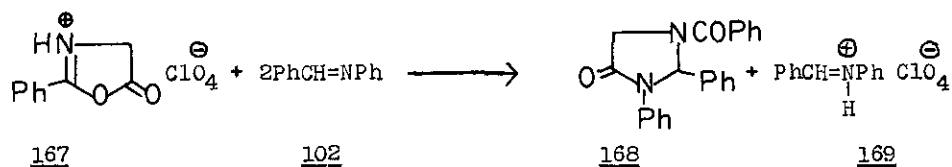
Recently, benzodioxinones were prepared by cycloaddition of o-chloranil (170) and 2-oxazolin-5-ones (32, R_1= Ph; R_2= H, alkyl or aryl)[131].
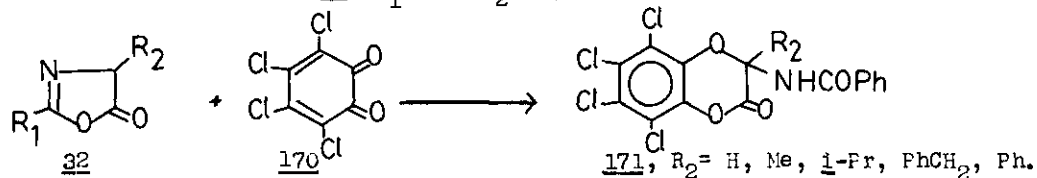
Thermolytic dimerisation of 32 to 172 should also be mentioned in this connection[132]. Similar dimerisation has been reported earlier[3].

172, R_1= i-Pr, n-Bu, i-Bu, 1-Bu, PhCH$_2$;
R_2= Ph
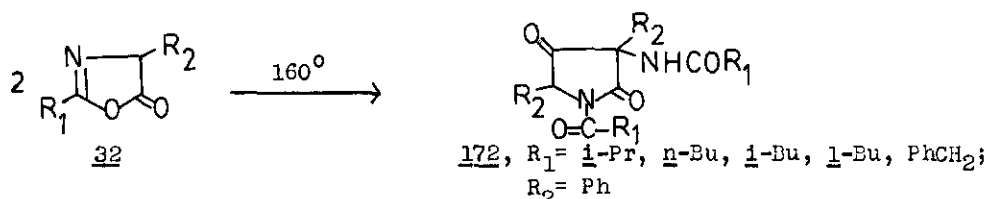
3.3. Miscellaneous Reactions:

3.3.1. Reactivity of the Side-Chain

The methyl group in 4-benzylidene-2-methyl-2-oxazolin-5-one (173) condenses with benzaldehyde to give the corresponding 2-styryl derivative 174[133]. Recently, this condensation was carried out with Schiff bases in glacial acetic acid containing a catalytic amount of fused sodium acetate, and the reaction led to the formation of 4-benzylidene-2-styryl-5-imidazolones (178)[134]. These compounds can exist as *cisoid-* and *transoid*-conformers.

Chlorination of 173 in a mixture of acetic acid and acetic anhydride gave the *pentachloro-acetoxy compound* 177[135], but halogenation in acetic anhydride alone or in carbon tetrachloride afforded the dihalo compound 179 (Scheme 26)[136].

The methyl group in 4-isopropylidene-2-phenyl-2-oxazolin-5-one (180) is also reactive and it condenses with benzaldehyde. On reaction with N-bromosuccinimide the bromo compound 182[2,3] is given (Scheme 27).

Scheme 26
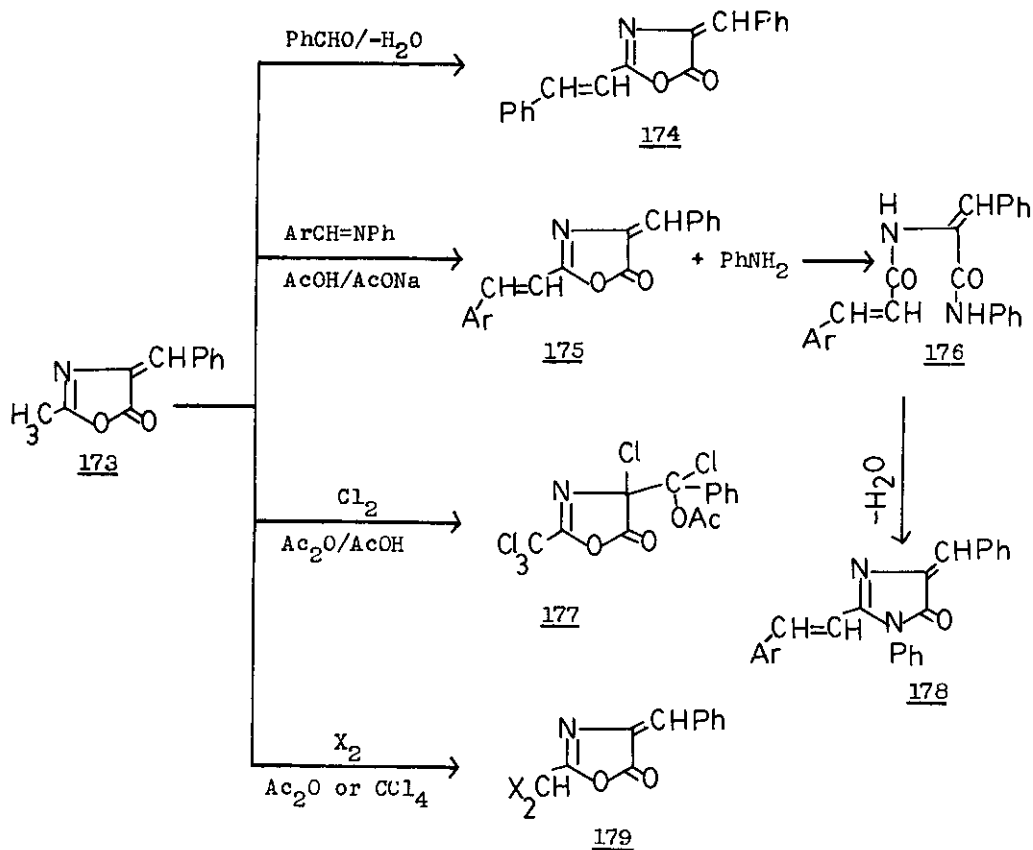
Scheme 27
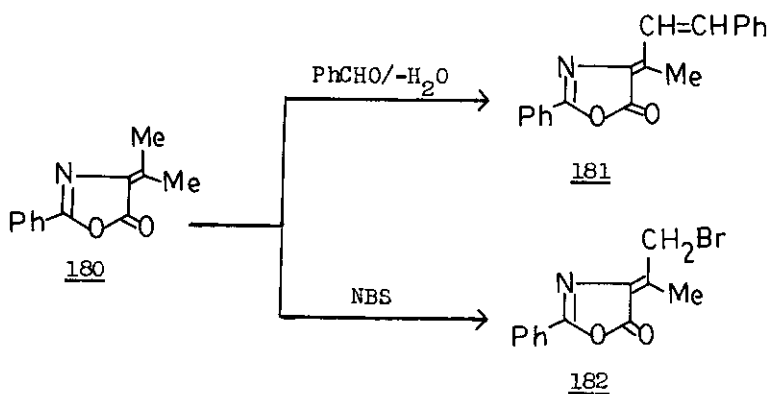
Friedel-Crafts and Grignard reactions with 4-alkylidene(arylidene)-2-oxazolin-5-ones may affect the olefinic centre. Also, the 4-C=C bond is

amenable to manipulation which has already been discussed.

3.3.2. Reactions with Oxygen

Oxygenation of 2-oxazolin-5-ones has been reported in recent years by several workers. For example, 2-oxazolin-5-one ($\underline{32}$, R_1= PhCH$_2$; R_2= Ph) in methanol, under an oxygen atmosphere, afforded $\underline{183}$[137]. On the other hand, Rose Bengal (R.B.) sensitised photooxygenation of $\underline{32}$ (R_1= Ph; R_2= Ph or PhCH$_2$) led to the formation of the imide ($\underline{185}$)[92], in moderate yield, through the adduct $\underline{184}$ obtained by 1,3-dipolar cycloaddition (Scheme 28).

Scheme 28

$\underline{183}$, R_1= PhCH$_2$; R_2= Ph

$\underline{185}$, R_1= Ph; R_2=Ph or PhCH$_2$
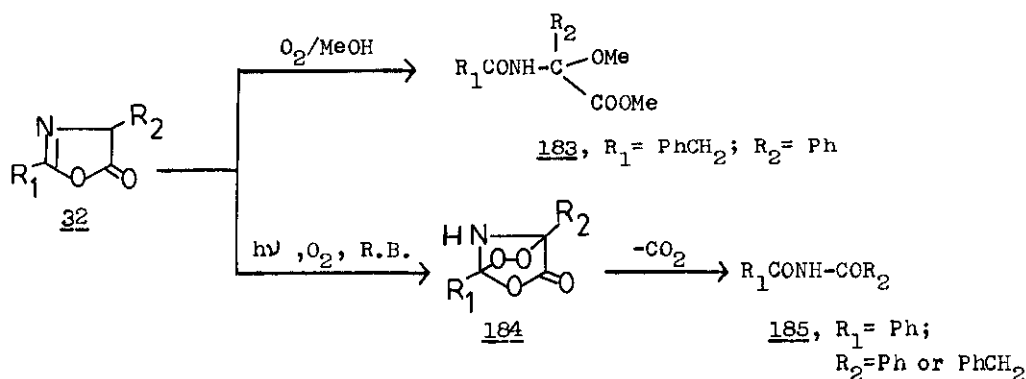
4-Benzylidene-2-oxazolin-5-one ($\underline{186}$, R = Ph) under similar conditions is cleaved by the solvent (Scheme 29)[92]. However, $\underline{186}$ (R = Me$_2$CH) rapidly absorbs oxygen at room temperature in the presence of triethylamine affording the imide ($\underline{188}$)[138]. Several intermediates were envisioned in the process.

Scheme 29

$\underline{187}$

$\underline{188}$
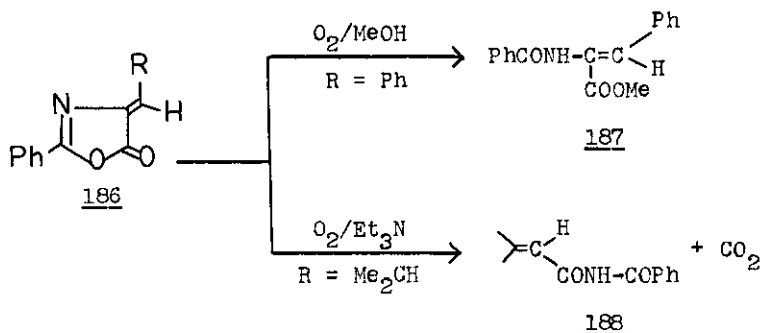
3.3.3. Fragmentation

As already described, some cycloadducts derived from 2-oxazolin-5-ones

undergo decarboxylation leading to various products. There are several
2-oxazolin-5-ones which are prone to thermal or photo fragmentation. For example,
4-acyl-2-oxazolin-5-ones (<u>57</u>) on heating undergo cycloelimination of carbon
dioxide affording oxazoles (<u>189</u>) in high yield. Also, 2-acyl-3-oxazolin-5-ones
(<u>190</u>) ungergo similar transformation (Scheme 30)[139]. Alternatively, 4-acyl-
2-oxazolin-5-ones can be easily hydrolysed and decarboxylated and the resultant
∝-acylamino ketones can be converted into oxazoles by cyclodehydration, and into
imidazoles through cyclisation of the corresponding ∝-acyl(aroyl)amino ketimines
and hydrazones.

Scheme 30

R_1= Me or Ph; R_2= Me or Me_2CH;   <u>189</u>
R_3= Me, Ph, MeO or CO_2Et

<u>57</u>,

<u>190</u>, R_1= Me or Ph; R_2= Ph or CF_3; R_3= Me, Ph, MeO
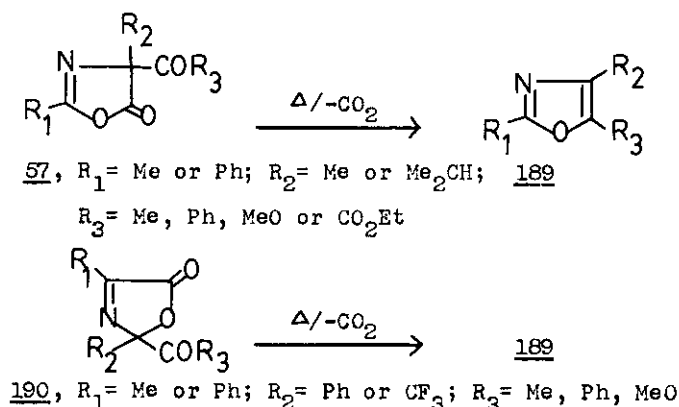
When 4-allyl-2-oxazolin-5-ones (<u>191</u>) were heated at 230°, Cope's rearrange-
ment followed by cycloelimination of carbon dioxide occurred, leading to the
formation of pyridine derivatives (Scheme 31)[140].

Scheme 31

R_1= i-Pr; n-Bu, i-Bu, Ph; R_2= Ph, i-Pr, MeCOCH_2
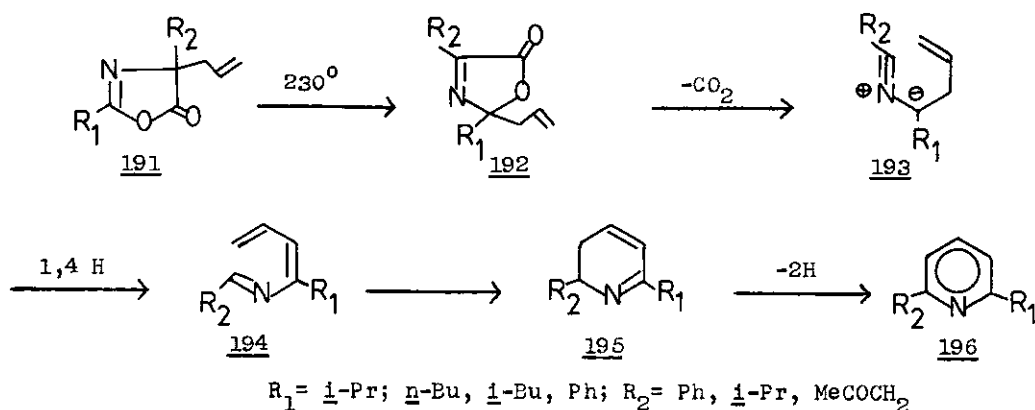
Photolysis of <u>197</u> in acetonitrile containing methyl acrylate gives 26% of
the (Z)- <u>200</u>, 17% of the (E)- <u>200</u> and 7% of acetophenone, obviously through

elimination of carbon dioxide and generation of the nitrile ylide 198 which is trapped by the dipolarophile. It is noteworthy that the C-2 substituent influences the reaction. For example, photolysis of 197 (R = Me) results in the expulsion of carbon monoxide producing 202, irrespective of the presence or absence of dipolarophiles. Also, 197 (R = F_3C) on refluxing in xylene loses carbon monoxide affording 201 (Scheme 32)[141], whereas 197 (R = Me) remains unaffected under these conditions.

Recently, photofragmentations of 2,4-diphenyl-2-oxazolin-5-one (32, $R_1 = R_2 = Ph$)[92] and 4-benzylidene-2-benzyloxy-2-oxazolin-5-one (85)[16] were reported and in both these cases expulsion of carbon monoxide is encountered (Scheme 33).

Scheme 32
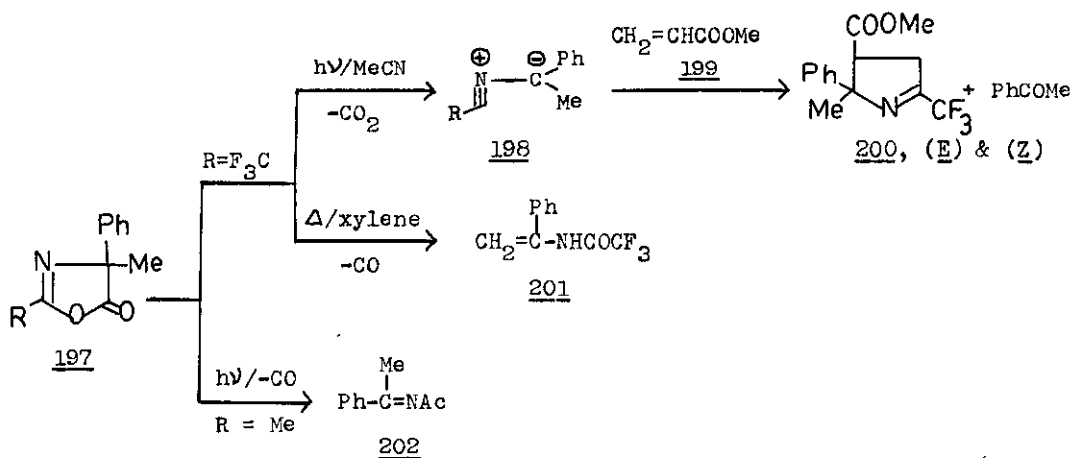
Scheme 33
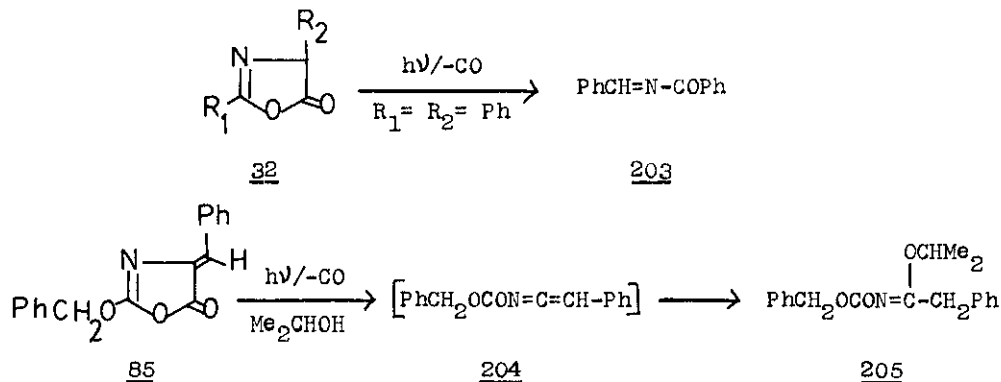
Fragmentation of suitable-2-oxazolin-5-ones has been profitably utilised in the synthesis of several useful intermediates. For example, 207, easily

obtainable from 206 through Cope's rearrangement, can be easily converted into 209 in very good yields[33]. This method was used for the chain elongation of several aromatic and heteroaromatic carboxylic acids (Scheme 34). Recently, similar route has been extended to the synthesis of δ-aminolevulinic acid derivatives and related compounds[82].

Scheme 34
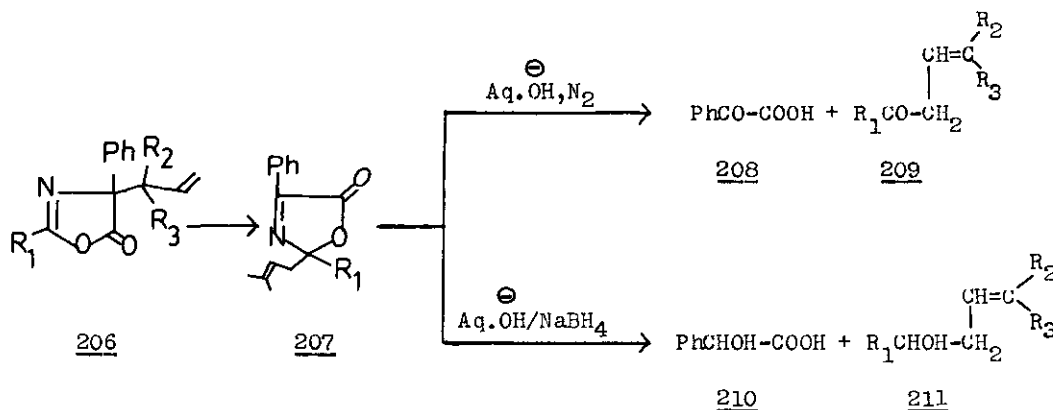
3.3.4. Formation of Oxazolo [5,4-b] Quinolines

Cyclisation of the nitro compound 212 with trialkyl phosphite gives the oxazolo[5,4-b]quinolines (213) which have CNS activity[142].

212, R = Ph or Me   213
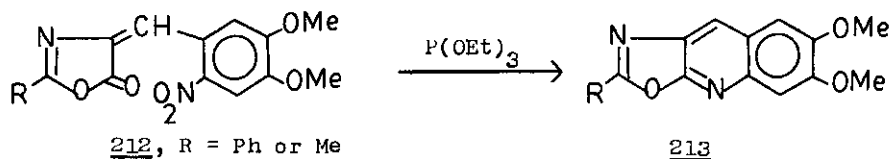
Conversion of 4-substituted 2-oxazolin-5-ones into other heterocycles is possible when 4-substituent carries a compatible vicinal functionality. Also, the steriodisposition around the double bond in 4-alkylidene(arylidene)-2-oxazolin-5-ones is important in this connection.

3.3.5. Biological Activity

In connection with penicillin research, antibacterial activity of this class of heterocycles was investigated[2] and a number of them was found to inhibit the growth of Staph. aureus at a dilution of less than 1:2000. Also, the tautomeric 2-oxazolin-5-one (27) was found to be active as antibacterial[22]. α-Amido-α, β-unsaturated acid esters, obtained by alcoholysis of 4-alkylidene-

(arylidene)-2-oxazolin-5-ones with chloroethanol and ethylene glycol, have been reported as potential bactericides[143].

4- [∝-(5-Nitro-2-furyl)-ethylidene] -2-oxazolin-5-ones were prepared as protozoal antiparasites[144]. Also, some similar furyl derivatives of 2-oxazolin-5-ones were synthesised as antifungal agents[145].

Contact sensitivity of rats to 2-oxazolin-5-ones, particularly 4-hetero-methylene derivatives has generated considerable interest, as is evidenced by several publications[146-151].

As already mentioned, many compounds derived from 2-oxazolin-5-ones exhibit biological activity. Thus, some amino acids were prepared as CNS inhibitors or alcoholism antagonists[152] and for treating Parkinsonism[153]. Also, a few 2-arylidene-2-imidazoline-5-ones, obtained by insertion of an amino moiety in · place of the oxygen atom in 2-aryl-4-arylidene-2-oxazolin-5-ones, are potentially important as antiinflammatory agents[154]. It is noteworthy that some products of aminolysis of 4-alkylidene(arylidene)-2-oxazolin-5-ones act as CNS inhibitors[155].

Recently, several 4-alkylidene(arylidene)-2-oxazolin-5-ones[156] and their dehydrooligopeptides[157] have been reported to exhibit antitumor activity with very low toxicity.

4. CONCLUDING REMARKS

As is evidenced by the foregoing discussion, the chemistry of 2-oxazolin-5-ones is a blossoming field, and there is enormous scope for using them in the synthesis of diverse compounds which may have application as synthons and/or as biologically active agents. Also, their utility in the field of polymers as well as dyes has not been thoroughly exploited. In view of the easy availability of starting materials for constructing these heterocycles and varieties of their reactions, they will continue to play important role as synthetic intermediates, and judicious application of the knowledge in this area will give the desired result.

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