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Reactions of 4,5-dihydro-5-oxo-1,3-oxazoles with oxygen-containing nucleophiles

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Contents

I.	Introduction	51
II.	Reactions with alcohols and phenols	51
III.	Reductive alcoholysis of unsaturated 5(4*H*)-oxazolones	57
IV.	Oxidative alcoholysis of 5(4*H*)-oxazolones	58
V.	Reactions with hydroxylamine derivatives and aminoalcohols	59
VI.	Intramolecular reactions of 5(4*H*)-oxazolones containing a hydroxy-group	61

Abstract. The literature data on the interaction of 4,5-dihydro-5-oxo-1,3-oxazoles with alkyl and aryl alcohols as well as aminoalcohols are surveyed. The intramolecular reactions of the oxazoles containing a hydroxy-group are examined. The bibliography includes 141 references.

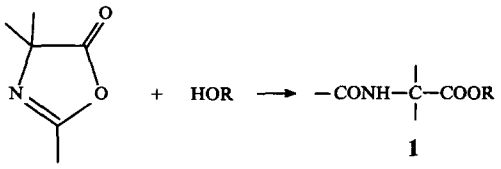
I. Introduction

Several reviews have been published since 1946 on the synthesis and chemical properties of 4,5-dihydro-5-oxo-1,3-oxazoles [(5(4*H*)-oxazolones)].[1–5] However, the reactions of 5(4*H*)-oxazolones with oxygen-containing nucleophiles are inadequately described in all these publications. Nevertheless, these reactions afford various compounds which are of both theoretical and practical interest.

At the present time, numerous studies devoted to the interaction of 5(4*H*)-oxazolones with oxygen-containing nucleophiles have accumulated in the literature. The aim of the present review is to survey the literature data on the interaction of both saturated and unsaturated 5(4*H*)-oxazolones with alcohols, phenols, aminoalcohols, and hydroxylamine derivatives. The intramolecular reactions of oxazolones containing a hydroxy-group are also discussed.

II. Reactions with alcohols and phenols

The reactions of 5(4*H*)-oxazolones with alkyl alcohols and aromatic alcohols proceed mainly with the cleavage of the 1,5-bond of the heterocycle, forming the corresponding esters of *N*-substituted aminoacids **1**:

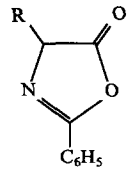


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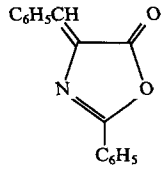
V O Topuzyan, N S Nesunts Laboratory of Synthesis of Biologically Active Derivatives of Aminoacids and Peptides, Institute of Fine Organic Chemistry, Academy of Sciences of the Republic of Armenia, 375014 Erevan, prosp. Azatutyan 26, Tel. (7-8852) 28 83 29

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In this process, saturated and unsaturated 5(4*H*)-oxazolones exhibit different reactivities. As a rule, saturated 5(4*H*)-oxazolones are more reactive than their unsaturated analogues. 4-Benzyl-2-phenyl-5-oxazolone **2** (R = $C_6H_5CH_2$ reacts smoothly at room temperature with methanol, forming the methyl ester of *N*-benzoylphenylalanine, whereas 4-benzylidene-2-phenyl-5-oxazolone **3** remains unchanged under similar conditions.[2]



2



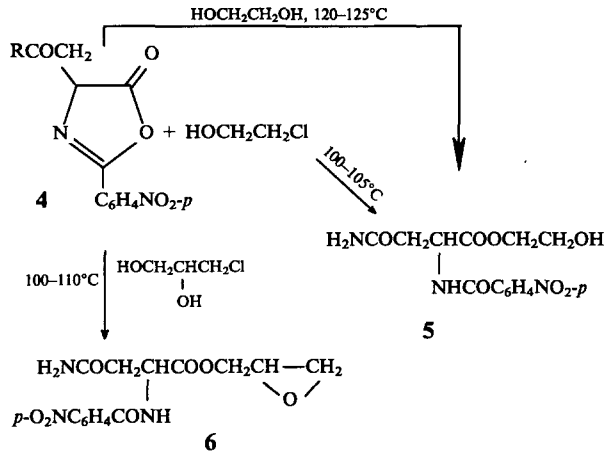
3

The inertness of unsaturated 5(4*H*)-oxazolones in relation to alcohols is indicated by their recrystallisation from ethanol, which has been described in most studies devoted to the synthesis of these compounds.

The rate of alcoholysis is also affected by the nature of the substituent in the 4-position in saturated 5(4*H*)-oxazolones. It has been noted[2] that the oxazolone **2** (R = $C_6H_5CH_2$) reacts with alcohols faster than 2-phenyl-5-oxazolones **2** (R = H), while 4-methyl-2-phenyl-5-oxazolone **2** (R = CH_3) reacts more slowly than the latter.

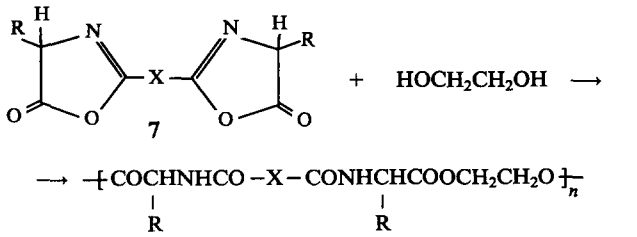
The alcoholysis also depends on the nature of the alcohol. Certain oxazolones react with methanol but are inert with respect to ethanol.[6] Secondary alcohols react with 5(4*H*)-oxazolones with difficulty, whilst tertiary alcohols frequently do not react at all.[4]

4-Carboxymethyl-2-(*p*-nitrophenyl-5-oxazolone **4** (R = OH) reacts with ethylenechlorohydrin at high temperatures (110 – 120 °C) to form the α-2-chloroethyl ester of *N*-*p*-nitrobenzoyl-DL-asparagine.[7,8] It is of interest to note that 4-aminomethyl-2-(*p*-nitrophenyl)-5-oxazolone **4** (R = NH_2) forms the 2-hydroxyethyl ester of the corresponding acid **5** under analogous conditions. The latter compound was also obtained by the reaction of the oxazolone **4** (R = NH_2) with 1,2-ethylene glycol.[7]

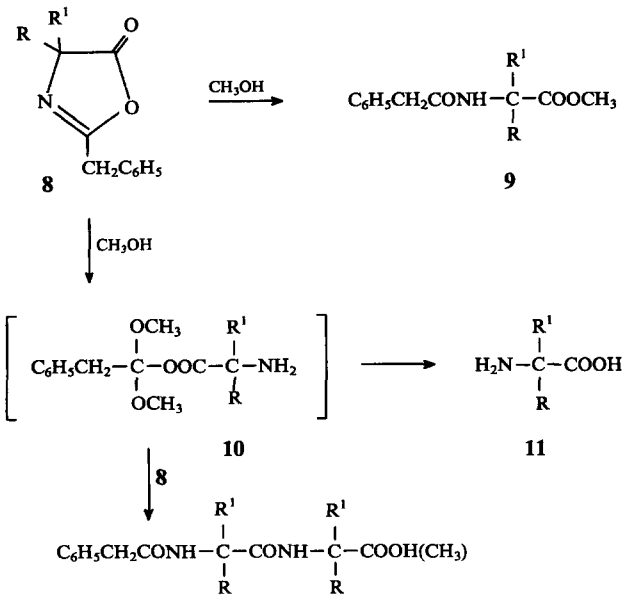


When the ratio of oxazolone **4** to ethylene glycol is 2:1 at 85–95 °C, the product of the reaction in dioxane is the bis-*O*-acylated glycol.[7] It was noted in the same communication that the oxazolone **4** (R = NH_2) reacts with glycerol-α-chlorohydrin [1-chloropropane-2,3-diol?] at high temperatures to form 2,3-epoxypropyl ether **6**.

The interaction of 2,2-bisoxazolones **7** with ethylene glycol at a temperature not exceeding 60 °C for 146 h leads to the formation of polymers:[9]

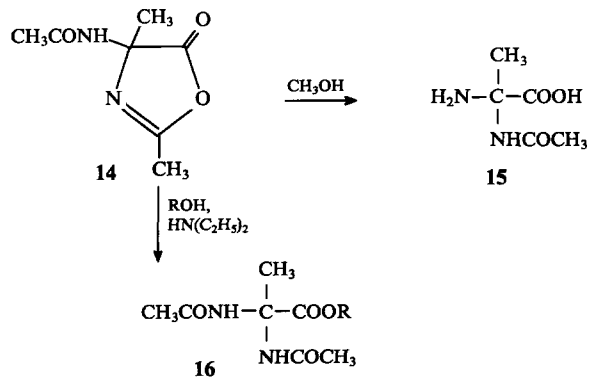


The reaction of unsaturated 5(4*H*)-oxazolones with ethylene glycol takes place at a higher temperature (150 °C).[10] Heating of glycerol containing 1–2% of an unsaturated 5(4*H*)-oxazolone to 200 °C leads to the formation of the monoglyceryl ester of a *N*-substituted aminoacid.[11,12]

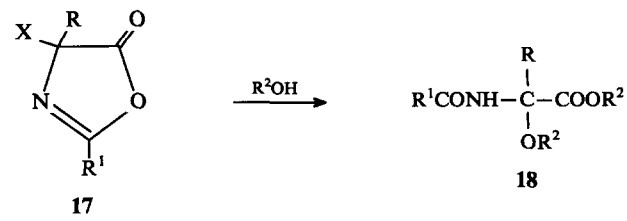


Certain saturated 5(4*H*)-oxazolones containing the benzyl substituent in the 2-position in the heterocycle behave in a non-standard manner on alcoholysis. Treatment of 2-benzyl-4-methyl-5-oxazolone **8** (R = H, R^1 = CH_3) or 2-benzyl-4,4-dimethyl-5-oxazolone **8** (R = R^1 = CH_3) with absolute alcohol does not, against expectation, lead to the formation of ester **9**. Under similar conditions, 2-benzyl-4-(*p*-methoxy-benzyl)-5-oxazolone **8** (R = H, R^1 = $CH_2C_6H_4OCH_3$-*p*) and 2-benzyl-4-isobutyl-5-oxazolone **8** [R = H, R = $CH_2CH\cdot(CH_3)_2$] not only undergo cleavage of the 1,5-bond with formation of the expected esters **9** but also react with the oxazolones as aminoalcohols with formation of the intermediate **10**. The latter can either decompose to the aminoacid **11** or its reaction with the oxazolone **8** can lead to the *N*-substituted dipeptide **12** or its ester **13**.[2]

The appearance of α-acetamidoalanine **15** in the methanolysis of 4-acetamido-2,4-dimethyl-5-oxazolone **14** is also explained by the formation of an intermediate analogous to compound **10**.[13] According to Nicolet,[14] the alcoholysis (methanolysis, ethanolysis) of the oxazolone **14** in the presence of diethylamine proceeds normally with formation of the ester **16**.

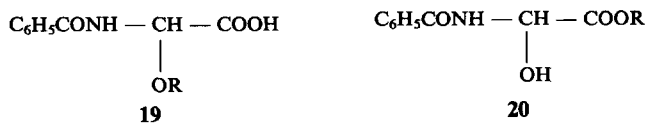


4-Halooxazolones **17** react smoothly with different alcohols.[15–20] The reaction with an excess of alcohol leads to the formation of *N*-substituted α-alkoxyaminoacids **18**. Under identical conditions the process proceeds with participation of both primary and secondary alkyl, arylalkyl, and alicyclic alcohols.[17]



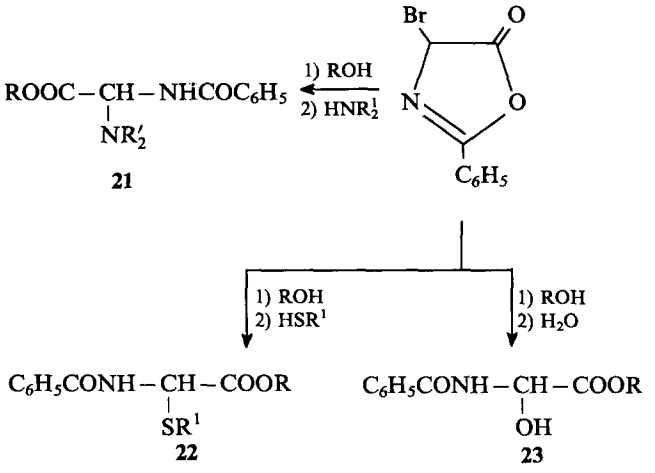
In the reaction of *tert*-butyl alcohol with 4-bromo-2-phenyl-5-oxazolone **17** (X = Br, R = H, R^1 = C_6H_5), *N*-benzoyl-α-*tert*-butoxyglycine **19** [R = $C(CH_{33}]$ and the *tert*-butyl ester of *N*-benzoyl-α-hydroxyglycine **20** [R = $C(CH_3)_3$] were obtained together with the *tert*-butyl ester of *N*-benzoyl-α-*tert*-butoxyglycine **18** [R = H, R^1 = C_6H_5, R^2 = $C(CH_3)_3$].

The analogous reaction with phenol leads to the formation of the phenyl ester of the aminoacid **20** (R = C_6H_5).[17] According to

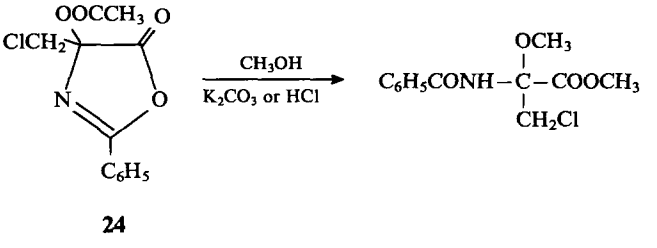


Chaman and co-workers,[15,17] the process under consideration, involving the alkoxides derived from alkyl alcohols, proceeds with greater difficulty than the reaction with the alcohols.

The study of the reaction of 4-halo-5(4*H*)-oxazolones with alcohols established[16,17] that opening of the oxazolone ring is proceeds faster than the substitution of the halogen atom by the alkoxy-group. This difference in reactivity has been used for the synthesis of esters of *N*-benzoylglycine with various substituents in the α-position compounds **21**–**23** (cf. Shemyakin and co-workers[17–20]).

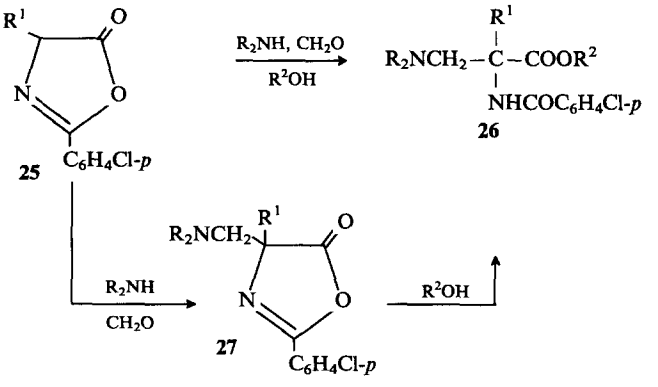


An α-alkoxyaminoacid ester is also formed in the reaction of 4-acetoxy-4-chloromethyl-2-phenyl-5-oxazolone **24** with methanol:[16]



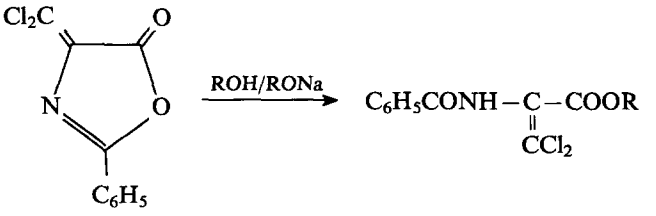
In the methanolysis of the oxazolone **24** in the presence of 10% potassium carbonate, the yield of the ester is 70%, whereas in the presence of hydrogen chloride the methanolysis proceeds with 50% yield. In the latter case, the corresponding α-methoxy-acid was also isolated from the reaction mixture in 15% yield.

The dialkylaminomethyl group in the 4-position of the saturated 5(4*H*)-oxazolone promotes alcoholysis. Under the conditions of the Mannich reaction,[21,22] carried out in methanol or ethanol, the oxazolone **25** gives rise to the formation of esters of 2-*N*-acylamino-3-dialkylaminopropionic acid **26**:



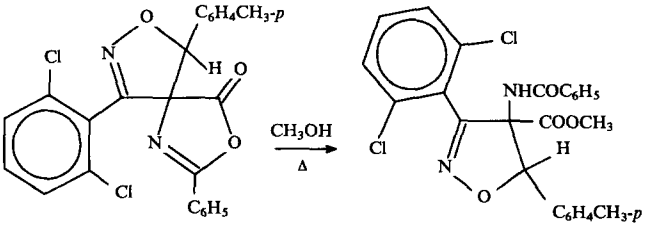
It was established that the product of the Mannich reaction — the oxazolone **27** — undergoes the ring opening reaction,[22] whereas according to other data[21] 2-*p*-chlorophenyl-5-oxazolones **25** are inert in relation to ethanol.

The alcoholysis of 4-dichloromethylene-2-phenyl-5-oxazolone **28** takes place on refluxing for up to 30 h with aliphatic alcohols (methanol, ethanol, isopropyl alcohol).[23] The process is accelerated in the presence of sodium alkoxides[24] but the substitution of halogen atoms is not then observed:



This phenomenon has been explained with the aid of Pearson's principle of hard and soft acids and bases (HSAB). Evidently the electrophilic centres in the oxazalone **28** — the carbon atoms of the dichloromethylene group and the carbon atom of the carbonyl group — clearly differ in their 'hardness'. The hard nucleophile — the alkoxide anion — therefore prefers to interact with the hard electrophilic centre located on the carbonyl group.[24]

4-Hydroxymethylene-2-phenyl-5-oxazolone readily undergoes alcoholysis by *p*-methoxybenzyl and 2,2,2-trichloroethyl alcohols when a benzene solution of the oxazolone and the corresponding alcohol are refluxed.[25] The spiro-oxazolones **29** also exhibit properties characteristic of 5(4*H*)-oxazolones; on refluxing, they react with methanol, affording the corresponding esters **30**:[26]



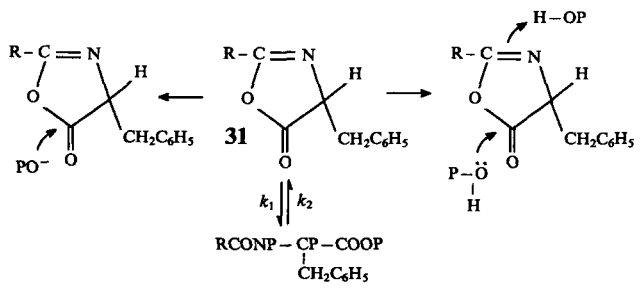
Among phenols, phenol itself and β-naphthol interact readily with 5(4*H*)-oxazolones.[27]

The reaction of saturated 5(4*H*)-oxazolones with phenols, especially *p*-nitrophenol, is also of theoretical importance in the study of the stereospecificity of peptide synthesis by the method of activated esters. One of the pathways leading to the racemisation of *N*-acylaminoacids in the formation of a peptide bond involves the intermediate formation of 5(4*H*)-oxazolones.[28] The question of both the formation of 5(4*H*)-oxazolones and of the opening of the oxazolone rings under the conditions of peptide synthesis has therefore become important. A number of studies have been devoted to such questions.[29–31]

The relative reactivities of 4-benzyl-2-benzyloxycarbonylaminomethyl-5-oxazolone **31** (R = $C_6H_5CH_2OCONHCH_2$) in relation to *p*-nitrophenol, dinitrophenol, and pentafluorophenol have been investigated.[29,30] According to Kovacs, et al.,[30] the above phenols can be arranged in the following sequence in terms of descending rate of opening of the oxazolone **31** ring: dinitrophenol, pentachlorophenol, *p*-nitrophenol. In all cases the rate of reaction depends on the phenol concentration. In the presence of triethylamine the series becomes *p*-nitrophenol, pentachlorophenol, dinitrophenol. Whereas in the absence of a tertiary amine the reactivity of phenols increases with enhancement of their acid properties, in the presence of triethylamine the opposite behaviour is observed. On this basis, one may conclude that the mechanisms of the opening of the oxazolone **31** ring by phenols and phenoxide anions differ.[29,30]

Thus the acidity of the phenols affects both the rate and the mode of the alcoholysis of 5(4*H*)-oxazolone. The comparatively less acid *p*-nitrophenol reacts slowly with the oxazolone **31**, as a result of which the resulting ester is racemic.[30]

Similar results were obtained in a study of the reaction of 4-benzyl-2-phenyl-5-oxazolone **31** (R = C_6H_5) with *p*-nitrophenol in the presence of tributylamine.[31] The determination of the rate constants for the forward (k_1) and reverse (k_2) reactions in the formation of the ester **32** (P = *p*-$NO_2C_6H_4$) for oxazolone : phenol : amine ratios of 1 : 10 : 10 shows that the equilibrium is displaced towards the formation of the ester.[31]



32

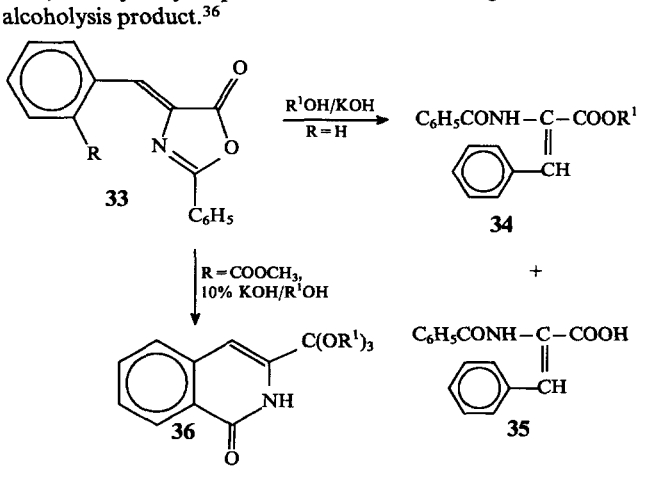
The kinetics of the reactions of 2-phenyl-5-oxazolone with substituted phenoxide anions have been investigated.[32]

p-Nitrophenyl *N*-benzamidoisobutyrate was obtained by the reaction of 4,4-dimethyl-2-phenyl-5-oxazolone with *p*-nitrophenol in the presence of triethylamine.[33] According to Suh et al.,[34] phenol reacts smoothly at pH 7 with unsaturated 5(4*H*)-oxazolones.

The reactions of oxazolones with alcohols and phenols are catalysed by both bases and acids.

Potassium[10, 35–38] or sodium[10, 39–44] hydroxides have been used to catalyse the alcoholysis of unsaturated 5(4*H*)-oxazolones. There have also been studies where alkali metal salts were used for this purpose: potassium[45] and sodium[42, 46–48] carbonates and also sodium acetate[49, 50] and tetrahydroborate.[51] Evidently in all cases the reaction is accelerated by the alkoxide ion generated under these conditions, which leads to the cleavage of the 1,5-bond of the oxazolone ring. According to Tripathy and Mikerjee,[36] in the case of unsaturated 5(4*H*)-azlactones the addition of the alkoxide anion to the exocyclic double bond is not observed.

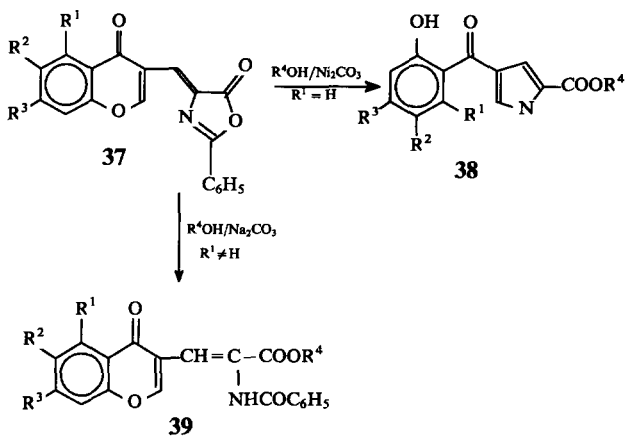
Analysis of the literature data shows that the amount of alkali used can affect the nature of the final products. The reaction of 4-benzylidene-2-phenyl-5-oxazolone **33** (R = H) with ethanol in the presence of catalytic amounts of potassium hydroxide leads to the formation of the ethyl ester of *N*-benzoyl-α,β-dehydrophenylalanine **34** (R^1 = C_2H_5 in a high yield. When an equivalent amount (in relation to the oxazolone) of alkali is used, the hydrolysis product **35** is detected together with the alcoholysis product.[36]



33 **34** **36** **35**

According to Stiller's data[35] the formation of only the acid **35** is observed in the reaction of the same oxazolone **33** (R = H) with a 10% alcoholic solution of potassium hydroxide. Evidently an increase in the amount of potassium hydroxide increases the concentration of hydroxide anions, increasing thereby the possibility of the competing reaction — the hydrolysis of the oxazolone. The formation of the ester **34** (R^1 = CH_3) and the acid **35** is also observed in the methanolysis of the oxazolone **33** (R = H) in a methanol – 1 M sodium hydroxide solution at room temperature.[43]

It is of interest to note that, in the presence of 10% potassium hydroxide in methanol or ethanol, 4-(*o*-methoxycarbonylbenzylidene)-2-phenyl-5-oxazolone **33** (R = $COOCH_3$) gives rise to the orthoformate **36** (R = CH_3 or C_2H_5).[35] The effect of the nature of the substituent in the 4-position on the product of the alcoholysis of 5(4*H*)-oxazolone is also observed in the reactions of unsaturated oxazolones **37** with alcohols (methanol, ethanol) in the presence of sodium carbonate.[46] Depending on R^1 in the benzene ring of the chromone residue of the oxazolone **37**, the reaction product can be the pyrrole **38** or the ester of the corresponding acid **39**:



37 **38** **39**

It has been noted[46] that both the oxazolone **37** and the ester **39** are converted into the pyrrole **38** on refluxing in the presence of sodium methoxide regardless of R^1.

The results of a study carried out to determine the optimum conditions for the alcoholysis of a series of unsaturated 5(4*H*)-oxazolones in the presence of ethylene chlorohydrin and ethylene glycol have been published.[10] It was established that in the case of ethylene chlorohydrin it is necessary to avoid a high concentration of the hydroxide anion (a 5% KOH solution is optimal), while in the case of ethylene glycol base catalysis can be replaced by the corresponding increase in temperature.

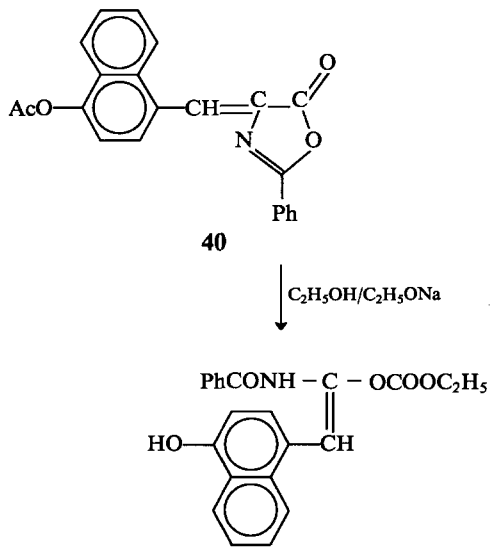
The influence of the electronic effects of the substituent in the 4-position in unsaturated 5(4*H*)-oxazolones on the rate of base-catalysed alcoholysis has been investigated.[39]

One of the common ways of catalysing the reactions of unsaturated 5(4*H*)-oxazolones with aliphatic alcohols is the method involving the use of the alkoxides derived from the same alcohols. The reaction proceeds mainly with the formation of the alkyl esters of *N*-substituted α,β-dehydroaminoacids with satisfactory results.[2, 24, 42, 46, 52–74]

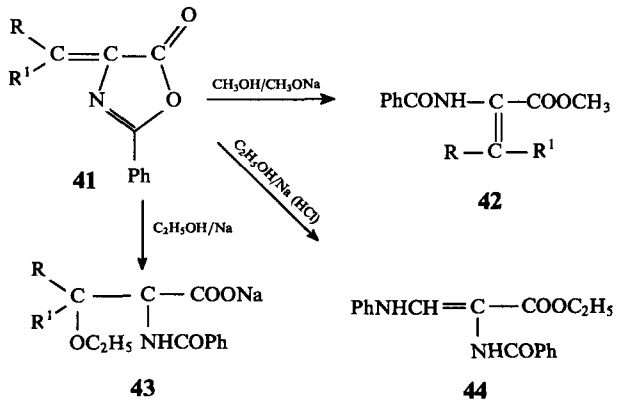
The ethanolysis of 4-[(4-acetoxy-1-naphthyl)methylene]-2-phenyl-5-oxazolone **40** in the presence of sodium ethoxide proceeds with simultaneous deacylation.[72]

It has been established[56] that the reaction of 4-isopropylidene-2-phenyl-5-oxazolone **41** (R = R^1 = CH_3) with methanol in the presence of sodium methoxide at pH 8.5 at room temperature is completed quantitatively after 4 h, whereas at 80 °C it leads to the formation of the methyl ester **42** (R = R^1 = CH_3) in 60% yield after 0.5 h. According to Zubareva et al.,[57] the methanolysis of the same oxazolone in the presence of comparatively small amounts

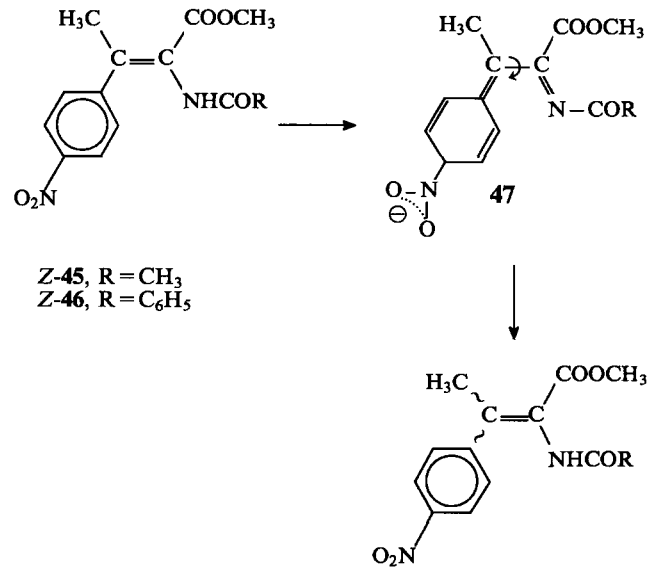
of sodium alkoxide leads to the expected ester **42** in 60% yield at room temperature after 20–25 h.



Cases are known where in the presence of sodium alkoxide the alcohol not only cleaves the 1,5-bond of the unsaturated 5(4*H*)-oxazolone but also adds to the exocyclic double bond of the heterocycle.[2, 4] 4-Ethylidene-2-phenyl-5-oxazolone **41** (R = H, R^1 = CH_3) is stable in boiling ethanol for 88 h. However, in the presence of sodium ethoxide the product was ethyl α-benzamido-β-ethoxybutyrate **43** (R = H, R^1 = CH_3).[2] The alkoxy-group in the 4-position increases the stability of the oxazolone ring in relation to alcohols.[4] However, according to the data quoted by Conforth,[2] the 2-phenyl-4-phenyl-4-phenylaminomethylene derivative **41** (R = H, R^1 = C_6H_5NH) reacts readily with ethanol in the presence of sodium ethoxide, giving rise to the ester of α-benzamido-β-phenylaminoacrylic acid **44**.[55]



One of the important questions concerning the alcoholysis of unsaturated 5(4*H*)-oxazolones is that of the configuration of the double bond in the reaction products. The study of this problem established[62] that reactions of *Z*- and *E*-4-arylethylidene-2-phenyl-5-oxazolones **41** (R = Ar, R^1 = CH_3) with sodium methoxide in methanol involve the stereospecific opening of the oxazolone ring with formation of the methyl esters of the corresponding *Z*- and *E*-acids. The same effect has been observed for 4-isobutylidene-2-phenyl-5-oxazolone **41** (R = C_2H_5, R^1 = CH_3) [56, 57] or 2-methyl(phenyl)-4-thienylmethylene-5-oxazolone **41** (R = thienyl, R^1 = H).[58, 68] However, in the case of *Z*-4-(α-*p*-nitrophenylethylidene)-2-phenyl-5-oxazolone **41** (R = 4-$NO_2C_6H_4$, R^1 = CH_3) the initial oxazolone isomer isomerises to form a mixture of the *Z*- and *E*-isomers of the expected ester with the *E*-isomer predominating.[62] The isomerisation of the *p*-nitrophenyl derivatives **45** and **46** can be explained by the fact that under alkaline reaction conditions the quinonoid compound **47**, in which rotation about the C–C bond becomes possible, may be formed:

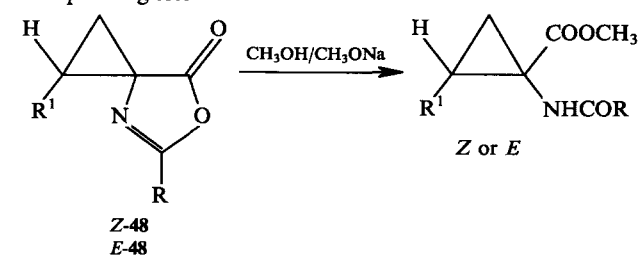


This conclusion is confirmed by the finding that the alcoholysis of the oxazolone *Z*-**46** in the presence of catalytic amounts of sulphuric acid proceeds without isomerisation.[62]

It is of interest to note that *Z*-4-benzylidene-2-phenyl-(methyl)-5-oxazolone **41** (R = H, R^1 = C_6H_5) undergoes alcoholysis in the presence of sodium alkoxide without change in the conformation of the double bond. However, the *E*-isomer leads to the formation of a mixture of the *Z*- and *E*-alkyl esters of *N*-substituted α,β-dehydrophenylalanine **42** (R = C_6H_5, R^1 = H) under the same conditions with the *Z*-isomer predominating.[53, 62]

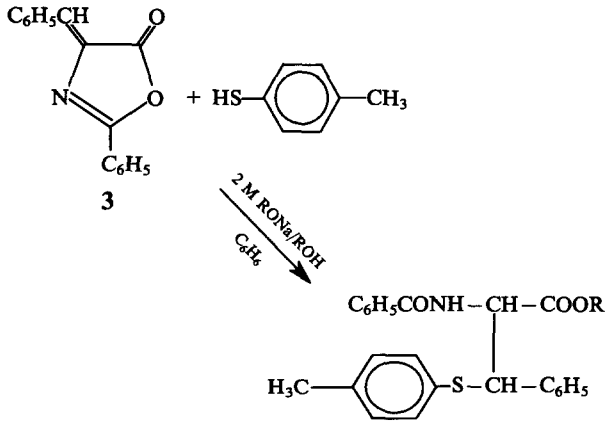
The alcoholysis of 4-(*p*-dimethylaminobenzylidene)-2-phenyl-5-oxazolone **41** [R = H, R^1 = 4-$(CH_3)_2NC_6H_4$] in the presence of alkali (NaOH) proceeds stereoselectively, while acid alcoholysis leads to the formation of a mixture of two geometrical isomers of the unsaturated ester **42** [R = H, R^1 = 4-$(CH_3)_2NC_6H_4$].[44]

The spiro-oxazolones **48** having both the *E*- and *Z*-conformations readily react with absolute methanol in the presence of catalytic amounts of sodium methoxides, being converted into the corresponding esters:[66, 67]



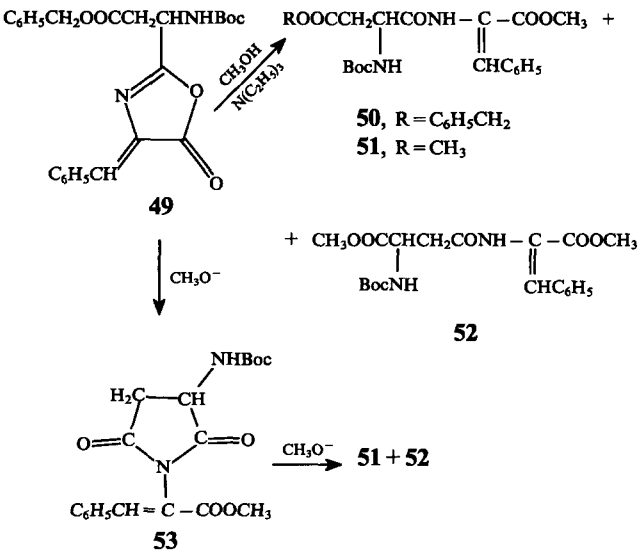
Z-**48**
E-**48**

It has been shown[2, 53] that the reaction of the oxazolone **3** with tolylmercaptan in the presence of sodium methoxide proceeds with formation of the corresponding ester of α-benzamido-β-phenyl-β-(*p*-tolylthio)propionic acids (see over):



The alcoholysis of 5(4*H*)-oxazolones also occurs in the presence of organic bases — amines. Both secondary[13] and tertiary[75–78] amines have been used for this purpose.

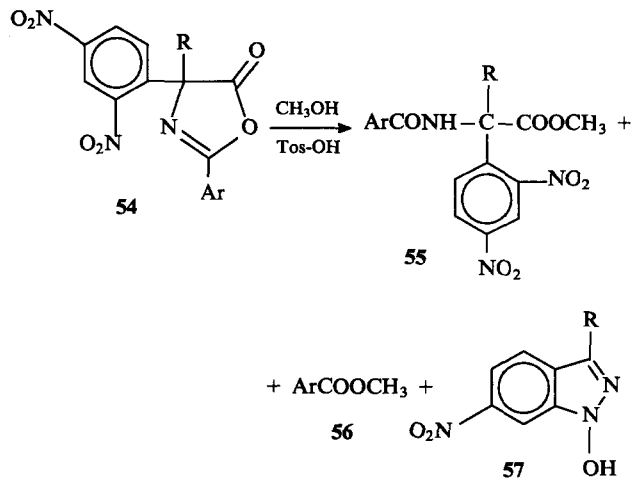
The methanolysis of the oxazolone **49** in the presence of triethylamine does not proceed unambiguously.[76] It affords a mixture of three compounds — the benzyl ester **50** and the methyl esters **51** and **52**. Evidently when the oxazolone ring is opened at the 1,5-bond on treatment with the nucleophile, the succinimide **53** is formed and leads to the formation of the unexpected methyl esters **51** and **52**.



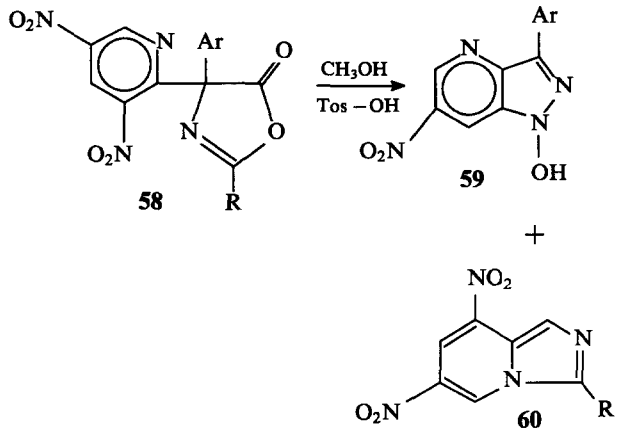
It has been noted[76] that the methanolysis of the oxazolone **49** in the presence of equimolar amounts of 4-dimethylaminopyridine leads unambiguously to the desired ester **50** without side products.

The opening of the oxazolone ring by alcohols is also catalysed by acids. Sulphuric acid,[79, 80] hydrochloric acid,[75, 81, 82] and toluene-*p*-sulphonic acid[83] have been used. In all cases the main reaction product is the alkyl ester of a *N*-substituted aminoacid.

According to D'Anello et al.,[83] on refluxing in methanol in the presence of catalytic amounts of toluene-*p*-sulphonic acid, 2-aryl-4-(*o*-nitrophenyl)-5-oxazolones **54** afford mixtures of methyl benzoate **56** and derivatives of 1-hydroxy-1*H*-indazole **57**. This reaction proceeds similarly also in ethanol and 1,2-ethylene glycol. However, in 2-propanol or *tert*-butyl alcohol, the main product is compound **57**. It is of interest to note that, both in the presence and absence of toluene-*p*-sulphonic acid in methanol, the oxazolone **54** (R = *iso*-C_3H_7) gives rise to the methyl ester of the corresponding acid **55** (R = *iso*-C_3H_7).

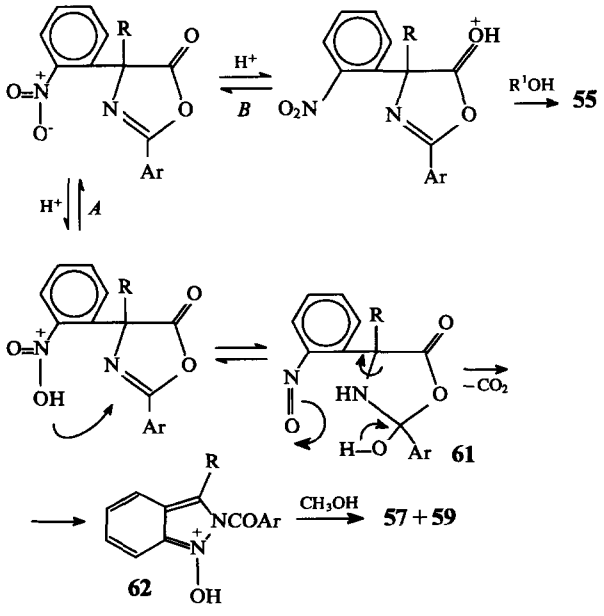


The reaction of 4-(β-nitropyridyl)oxazolones **58** with methanol in the presence of toluene-*p*-sulphonic acid has also been investigated.[83] It was established that the main reaction products are the indazole **59** and the imidazo[1,5-a]pyridine **60**:



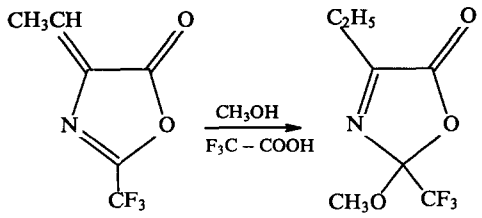
An ester analogous to compound **55** is formed in small amounts in this process.

The formation of compounds **57** and **59** can be explained by the nucleophilic attack by the oxazolone nitrogen atom on the protonated nitro-group (pathway *A*) with subsequent migration



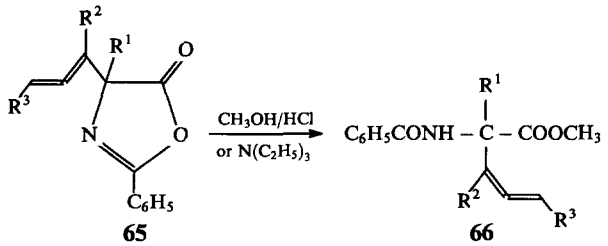
of the hydroxy-group to C(2) — an oxazolone carbon atom. After the evolution of carbon dioxide, the intermediate **61** formed in this process is converted into compound **62**, in which deacylation by the alcohol takes place with formation of compound **57** or **59**. The competing reaction — the catalytic opening of the oxazolone ring with formation of the aminoacid ester **55** (pathway *B*) — takes place simultaneously.

In the presence of trifluoroacetic acid, the reaction of a mixture of the *Z*- and *E*-isomers of 4-ethylidine-2-trifluoro-methyl-5-oxa-zolone **63** with methanol gives rise to the 1,4-adduct **64**:[84]



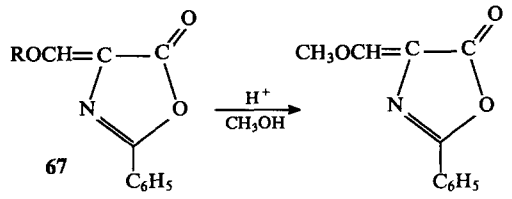
63 **64**

Methanolysis of the oxazolone **65** in the presence of hydrogen chloride leads to the formation of the corresponding ester **66** in a quantitative yield over a period of 15 min at room temperature. A similar result was obtained when the alcoholysis was carried out in the presence of triethylamine.[75]



65 **66**

In the presence of catalytic amounts of acid in methanol, the alkoxy-group of the alkoxymethyleneoxazolone **67** is substituted by the methoxy-group.[2]



67

The transalkylation of the alkoxy-group in compound **67** also proceeds in the presence of a platinum catalyst on heating with various alcohols.[85, 86]

The reactions of 5(4*H*)-oxazolones with epoxide resins proceed with ring opening.[87] The main products are the amidoesters containing the $-OOC-\overset{|}{C}-N-CO-$ fragment. The reaction in the absence of a catalyst is carried out at 190 °C. On the other hand the employment of catalysts usual for epoxide compositions makes it possible to reduce the reaction temperature to 140 – 150 °C. Both in the reactions with alcohols and in the case of the epoxide resins the chemical reactivity of 5(4*H*)-oxazolones depends on the polarity of the substituents in the 2- and 4-positions. Saturated 5(4*H*)-oxazolones react comparatively readily, while their unsaturated analogues require severe conditions.[87]

It has been shown[88, 89] that the reaction of saturated 5(4*H*)-oxazolones with hydroxylated polymers is catalysed by acids.

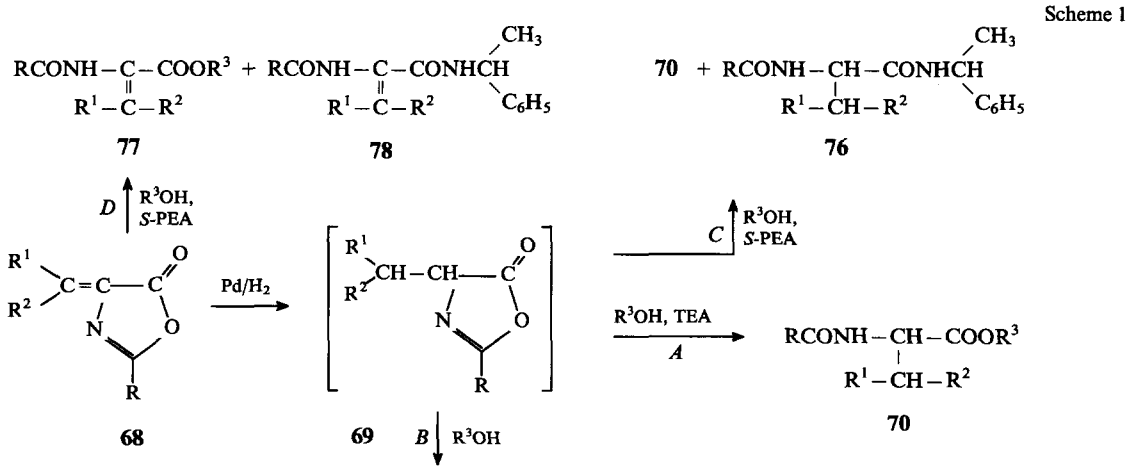
III. Reductive alcoholysis of unsaturated 5(4*H*)-oxazolones

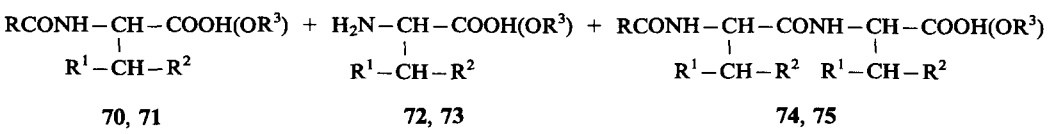
A group of workers[90–97] achieved a very successful catalytic hydrogenation of unsaturated 5(4*H*)-oxazolones in alcohols. The catalyst is palladium obtained by reducing $PdCl_2$ in situ. The hydrogenation is carried out in the presence of triethylamine (TEA),[91] (*S*-(–)-α-phenylethylamine (*S*-PEA),[90–96] and (*S*)-(–)-*N*,*N*-dimethyl-α-phenylethylamine (*S*MPA).[94] According to Neupokoeva et al.,[91] the reductive alcoholysis of unsaturated 5(4*H*)-oxazolones can proceed in accordance with Scheme (1).

The unsaturated oxazolone **69** is obtained during hydrogenation, leading to a mixture of products **70** – **75** in the absence of a base (pathway *B*). The formation of the diacylated aminoacids **72** and **73** and their condensation products **74** and **75** can be explained by the interaction of the alcohol with the C(2) atom of the oxazolone **69** [the analogous process with 5(4*H*)-oxazolones was described above]. With decrease in the acidity of the alcohol (CH_3OH > C_2H_5OH > *iso*-C_3H_7OH), the cleavage of the 1,5-bond of the oxazolone **69** intensifies and leads to the formation of aminoacid esters **70**. In the presence of tertiary amines (TEA, *S*-MPA) the alcoholysis with formation of the ester **70** becomes the main reaction pathway (pathway *A*).

In the presence of *S*-PEA, the opening of the saturated [compound **69**] and unsaturated [compound **68**] oxazolones can

Scheme 1

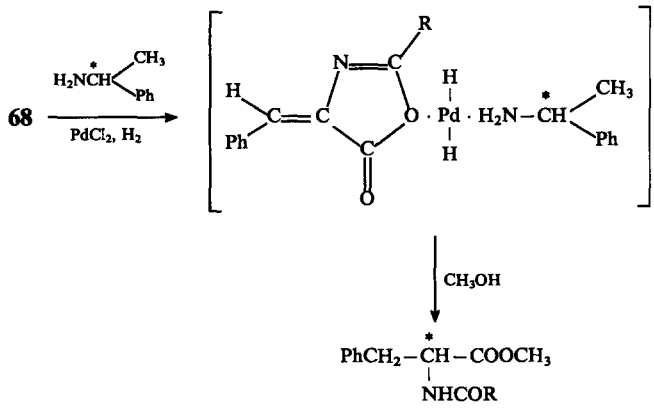




70, 71 **72, 73** **74, 75**

take place under the influence of both the primary amine and the solvent (pathways *C* and *D*). Under these conditions, mainly the acylaminoacid ester[70] forms in methanol (pathway *C*).[91, 93-95, 97] On passing to alcohols with a higher molecular weight and a greater degree of branching of the molecule (C_2H_5OH, C_3H_7OH, *iso*-C_3H_7OH, C_4H_9OH, *sec*-C_4H_9OH, *tert*-C_4H_9OH), the content of the amide **76** increases.[93, 94] Furthermore, in connection with the decrease in the rates of hydrogenation of the unsaturated oxazolone **68** in the presence of *S*-PEA, unsaturated reaction products—the ester **77** and the amide **78**—are detected in the catalytic reaction mixture (pathway *D*).[91]

Reductive alcoholysis in the presence of the chiral amine *S*-PEA leads to the (*R*)-configuration of the ester **70** in the case of 2-alkyl(aryl)-4-benzylidene-5-oxazolone **68** (R^1 = H, R^2 = C_6H_5) [90] and to the (*S*-enantiometer in the case of 4-benzylidene-2-phenyl-5-oxazolone **68** (R = C_6H_5, R^1 = H, R^2 = C_6H_5).[97] The formation of the optically active methyl esters **70**) in the reductive methanolysis shows that in alcohols there is a possibility of the interaction of the oxazolone **68** with the hydrogen on the surface of the palladium catalysts modified by the chiral amine *S*-PEA without the migration of the reaction into the bulk phase.[90, 91] It has been suggested[93] that, in the enantioselective reductive methanolysis of unsaturated 5(4*H*)-oxazolones, the oxazolone **68** initially assumes a definite orientation in relation to the hydrogenating centre under the steric control of the chiral *S*-PEA coordinated to the catalytic palladium complex. This is followed by the formation of a coordinate bond between palladium and compound **68** and then by the saturation of the double bond and the opening of the oxazolone ring, which takes place within the complex without the elimination of the intermediate compounds.



70

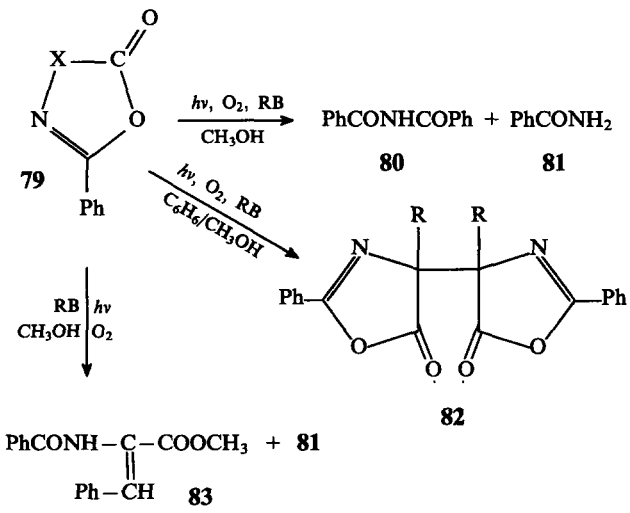
According to Khatskevich et al.,[94] the reductive methanolysis by the *Z*- and *E*-isomers of 4-*sec*-butylidene-5-oxazolones **68** (R^1 = CH_3, R^2 = C_2H_5) gives rise to the same diastereoisomeric composition of the aminoacid esters **70**. It follows from this that the *Z* – *E* isomerisation of the oxazolone **68** takes place in this process and that an identical mixture of isomers undergoes reduction. This is demonstrated by the finding that 4-*sec*-butylidene-5-oxazolone is not reduced in *tert*-butyl alcohol in the absence of a base and that the *Z*- and *E*-unsaturated oxazolones isomerise regardless of the initial compound **68**. In this case, the formation of *N*-substituted aminoacid esters takes place with a lower enantioselectivity than for 4-benzylidene-2-methyl-5-oxazolone **68** (R = CH_3, R^1 = H, R^2 = C_6H_5).[91] The reduction of both the *Z*- and *E*-isomers of 4-*sec*-butylidene-5-oxazolone in the presence of *S*-MPE leads to the optically active methyl ester **70** with a *threo* : *erythro* ratio of 63 : 67.[94]

When chiral phosphonic acid complexes of palladium are used as the catalyst, the double bond of the oxazolone **68** is hydrogenated initially and this is followed by the alcoholysis of the saturated oxazolone **69**.[97]

The reductive alcoholysis of unsaturated 5(4*H*)-oxazolones also proceeds in methanol in the presence of magnesium[98] or Raney nickel and sodium methoxide,[99] which leads to racemic methyl esters of *N*-substituted aminoacids.

IV. Oxidative alcoholysis of 5(4*H*)-oxazolones

Saturated and unsaturated 5(4*H*)-oxazolones react with alcohols in different ways in the presence of oxygen. The sensitised photochemical oxidation of 2,4-diphenyl-5-oxazolone **79** (X = CHC_6H_5) in methanol and in the presence of Rose Bengal (RB) for 0.5 h leads to the formation of 40% of the dibenzamide **80** (R = C_6H_5) and 49% of the benzamide **81**:



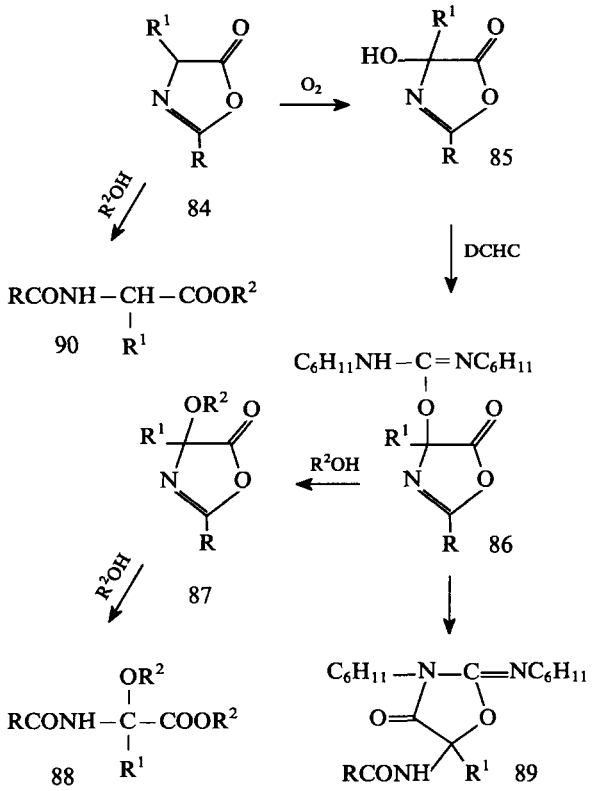
82

PhCONH–C(=CH–Ph)–COOCH$_3$ + **81**

83

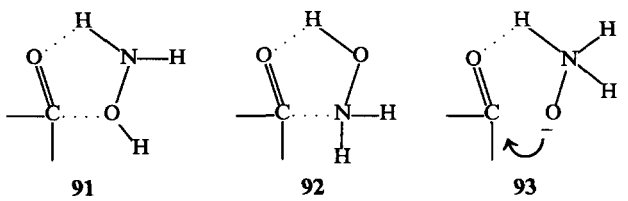
In a benzene–methanol mixture, the photochemical oxidation in the course of 0.25 h leads mainly to the formation of the dimer **82**.[100] Similar results were also obtained for 4-benzyl-2-phenyl-5-oxazolone **79** (X = $CHCH_2C_6H_5$), while, as in the case of its unsaturated analogue **79** (X = $C{=}CHC_6H_5$), the photochemical oxidation in the course of 0.25 h leads to the formation of a mixture consisting of 53% of the methyl ester **83** and 29% of the benzamide **81**.[100] When the photochemical oxidation of the unsaturated oxazolone **79** is prolonged to 0.75 h, the only product isolated from the reaction mixture is benzoic acid (yield 45%).

The interaction of the saturated oxazolones **84** with *N*,*N*-dicyclohexylcarbodiimide (DCHC) in methanol or ethanol and under an oxygen atmosphere also leads to the formation of a mixture of products.[101, 102] In the case of 2-benzyl-4-phenyl-5-oxazolone **84** (R = $CH_2C_6H_5$, R^1 = C_6H_5), the alkyl ester of α-alkoxy-*N*-phenylacetylphenylglycine **88** [R = $CH_2C_6H_5$, R^1 = C_6H_5, R^2 = CH_3 or C_2H_5 (37 and 27% respectively)], the alkyl ester of *N*-phenylacetylglycine **90** [R = $CH_2C_6H_5$, R^1 = C_6H_5, R^2 = CH_3 (7%)], and the oxazolone **89** [R = $CH_2C_6H_5$, R^1 = C_6H_5 (10% in methanol and 32% in ethanol)] were isolated from the reaction mixture.[102] It is suggested that the reaction proceeds via the oxidation of the oxazolone **84** to 4-hydroxy-oxazolone **85**, which interacts with DCHC to form the intermediate **86**. As a consequence of the attack by the alcohol, the latter gives rise to the ester **88** via compound **87** or undergoes an intramolecular rearrangement to compound **89**. When this reaction is carried out in 2,2,2-trichloroethanol, it leads to the formation of only the corresponding ester **90** (R = $CH_2C_6H_5$, R^1 = C_6H_5, R^2 = CH_2CCl_3). In the case of 2-benzyl-4-methyl-5-oxazolone **84** (R = $CH_2C_6H_5$, R^1 = CH_3), the oxidative alkoxylation product **88** is not detected, whereas in the case of 4-methyl-2-phenyl-5-oxazolone **84** (R = C_6H_5, R^1 = CH_3) compounds **88** and **90** (R = C_6H_5, R^1 = R^2 = CH_3) were isolated from the reaction mixture in 9% and 44% yields, respectively.[102]

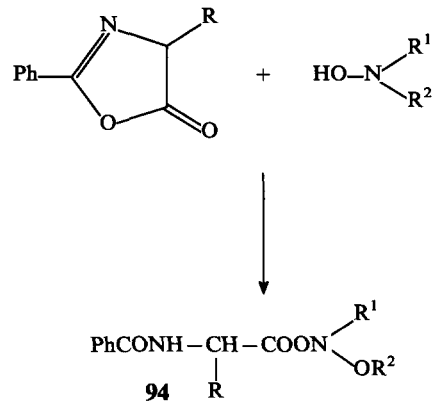


V. Reactions with hydroxylamine derivatives and aminoalcohols

Studies on the interaction of 5(4*H*)-oxazolones with hydroxylamine and its derivatives occupy a special place in the literature. The composition of reaction products is affected not only by the nature of the oxazolone but also by the reaction temperature and the solvent. Unsaturated 5(4*H*)-oxazolones react with hydroxylamine to form two products.[103] Evidently this entails the *N*- and *O*-acylation of hydroxylamine. In the presence of an excess of the latter, one product (the *O*-acyl derivative) vanishes. According to Goodman and Glaser,[103] hydroxylamine can attack 5(4*H*)-oxazolone along one of two pathways with the formation of products **91** and **92**. In addition, hydroxylamine can attack the 5(4*H*)-oxazolone in the form of the zwitter-ion **93**.



In the reaction of saturated 5(4*H*)-oxazolones with *N,N*-disubstituted hydroxylamine derivatives, the reaction product is an ester of the *N*-substituted aminoacid **94**.[103–105] According to the authors,[103] in the latter case a zwitter-ionic reaction mechanism takes place. Evidently, by virtue of the bifunctional attack by hydroxylamine and its derivatives, the opening of the oxazolone ring without racemisation becomes possible, particularly in the case of strong nucleophiles such as *N*-hydroxysuccinimide or 1-hydroxybenzotriazole, which have the properties of weak bases.[103–105]

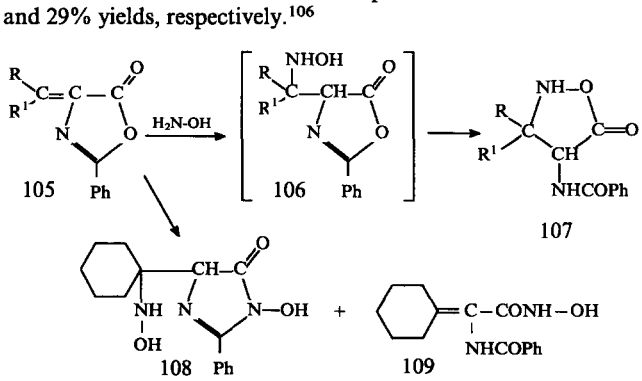


The reaction of hydroxylamine with unsaturated 5(4*H*)-oxazolones leads to different products. The reaction has been very effectively investigated by Ali and Khan.[106] Depending on the pH of the medium, the reactant ratio, the nature of the solvent, and temperature, different products are then obtained.

The hydroxamic acids **96** (26%) and **97** (51%) are obtained in the reaction of compound **95** (R = C_6H_5) with hydroxylamine at room temperature. When there is an excess of hydroxylamine, one obtains in the presence of sodium methoxide 20% of bis-(α-benzamidocinnamoyl)hydroxamic acid **101**, 4-(α-hydroxyaminobenzyl)-2-phenyl-5-oxazolone **99** (28%), 1-hydroxy-4-(α-hydroxyaminobenzyl)-2-phenyl-5-imidazolone **104** (35%), and 4-benzylidene-1-hydroxy-2-phenyl-5-imidazolone **98** (15%). The yield of the last product **98** increases sharply (to 58%) when pyridine is used instead of methanol. On heating hydroxylamine hydrochloride with the oxazolone **95** (R = C_6H_5) in acetic acid, compound **102** is obtained in 77% yield,[106] whereas in the presence of sodium hydroperoxide compound **100** is formed in 66% yield.[107] 4-Benzamido-4,5-dehydro-5-phenyl-5-isoxazolone **100** is formed in a high yield (76%) on exposure to light.[106] (see over)

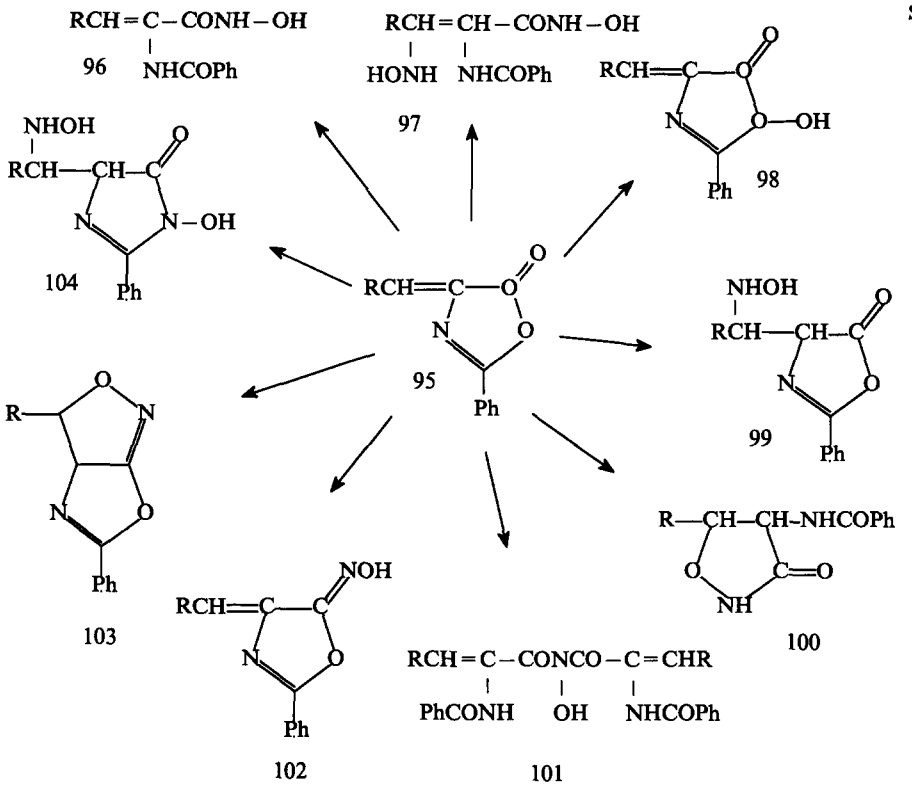
The reaction of hydroxylamine with 4-alkylidene-5-oxazolones **105** [107] proceeds, in contrast to 4-arylidene-5-oxazolones,[38] with formation of 3-alkyl-4-benzamido-5-oxo-1,2-oxazolidine **107**. The mechanism of this reaction involves[107] the addition, in weakly alkaline or neutral media, of a hydroxylamine molecule to the exocyclic double bond of the oxazolone, after which the resulting saturated oxazolone **106** undergoes intramolecular ring opening with formation of the isoxazolidine derivative.

The reaction involving 4-cyclohexylidene-2-phenyl-5-oxazolone **105** (R = R^1 = C_5H_{10}) in the presence of sodium methoxide in methanol affords a mixture of compounds **108** and **109** in 40% and 29% yields, respectively.[106]

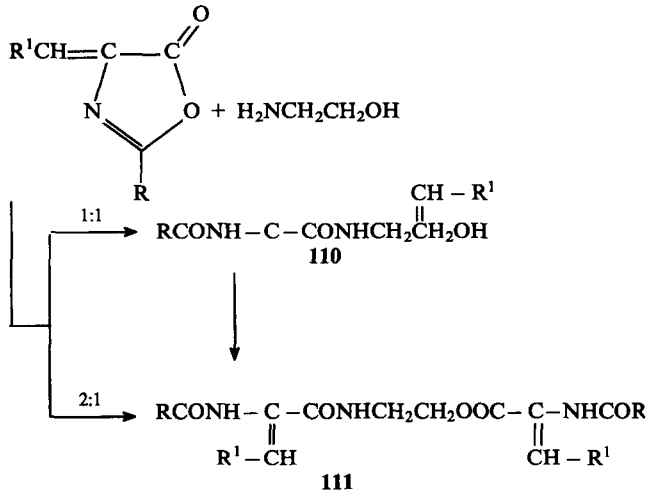


No studies on the reaction of unsaturated 5(4*H*)-oxazolones with *N,N*-di-substituted hydroxylamine derivatives have been described in the literature. However, there are communications devoted to the study of the reactions of these oxazolones with ethanolamine[108] and its derivatives.[109–121]

Scheme 2



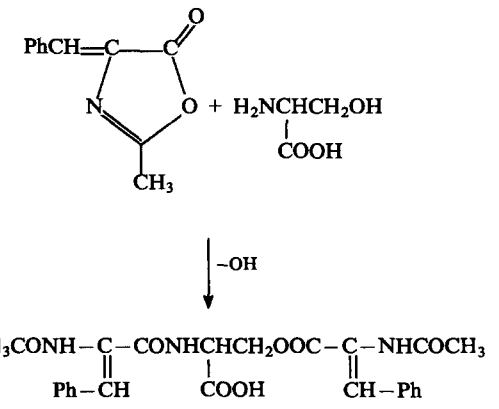
According to Lupsa,[108] owing to the comparatively high nucleophilicity of the amino-group, the interaction of equimolar amounts of monoethanolamine and an unsaturated 5(4*H*)-oxazolone leads to the formation of the 2-hydroxyethylamide **110**. On the other hand, when the oxazolone : aminoalcohol ratio is 2 : 1, the reaction product in the presence of 1–2% of a base (NaOH) is the *N,O*-diacylated aminoethanol **111**. Lupsa[108] also achieved the opening of the oxazolone ring by the 2-hydroxyethylamides **110** to give compound **111**.



The products of *N,O*-diacylation are also formed on reaction of 4-benzylidene-2-methyl-5-oxazolone with serine in the presence of alkali.[110, 111]

According to Botvinnik et al.,[110] saturated 5(4*H*)-oxazolones react with the hydroxy-group of *N*-benzoylserine or the ethyl ester of *N*-benzoylserine without ring opening.

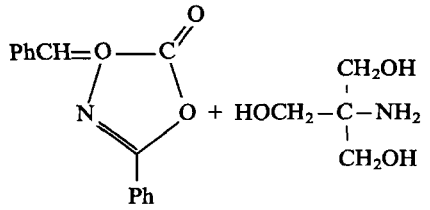
In the reactions of saturated 2,2-bis-5(4*H*)-oxazolones with ethanolamine, polymers with a regular structure have been obtained.[9]

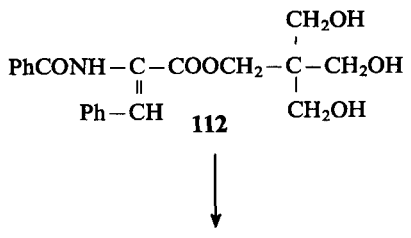


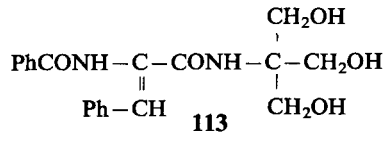
De Jersey and co-workers[112, 113] succeeded in isolating an ester of the α,β-dehydroaminoacid **112** in the reaction of the *Z*-isomer of 4-benzylidene-2-phenyl-5-oxazolone with tris-(hydroxymethyl)aminomethane in acetonitrile.It has been noted that the ester **112** is unstable, especially under alkaline conditions, and can be converted into the corresponding amide **113** as a consequence of an intramolecular rearrangement and an intermolecular interaction. The formation of an ester can be accounted for by the steric hindrance generated by the hydroxymethyl groups, on the one hand, and by the intramolecular hydrogen bond between the amino- and hydroxy-groups (which increases the nucleophilicity of the hydroxy-group), on the other.

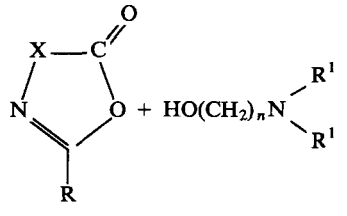
The interaction of dialkylaminoalkyl alcohols with both saturated,[114, 115] and unsaturated[115–118] 5(4*H*)-oxazolones leads to the formation of the corresponding esters of *N*-substituted aminoacids **115**.

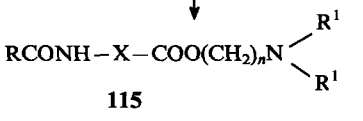
According to the data of Topuzyan et al.,[115] the reaction of the saturated oxazolone **114** (X = $CHCH_2C_6H_5$) with 2-dimethylaminoethanol takes place under milder conditions than the reaction with the unsaturated analogue **114** (X = $C{=}CHC_6H_5$). When *Z*-unsaturated 5(4*H*)-oxazolones are used, the heterocycle is opened stereoselectively by this aminoalcohol.[119]







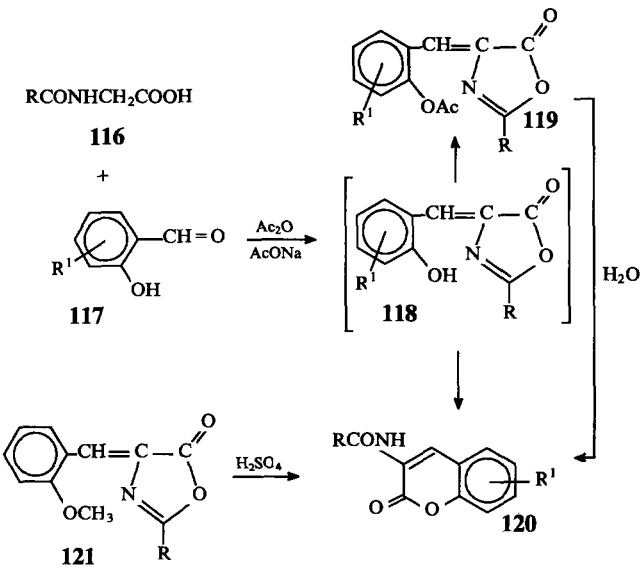




It has been established that the interaction of 2-dimethylaminoethanol with 4-benzylidene-2-phenyl-5-oxazolone involves general base catalysis.[120] The influence of the solvent[120] and certain additives (1-hydroxybenzotriazole, *N*-hydroxysuccinimide, imidazole, and *p*-nitrophenol)[121] on this reaction has been investigated. According to a patent,[118] the opening of the unsaturated oxazolone ring by dialkylaminoalkyl alcohols is accelerated in the presence of the alkoxides derived from the same aminoalcohols.

VI. Intramolecular reactions of 5(4*H*)-oxazolones containing a hydroxy-group

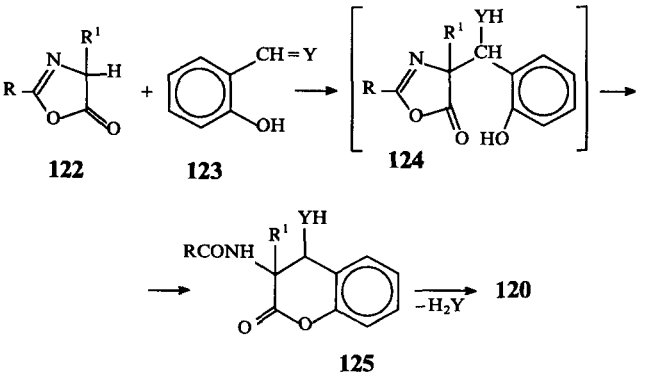
The synthesis of unsaturated 5(4*H*)-oxazolones from *N*-acylglycine **116** and derivatives of salicylaldehyde **117** involves the formation, under the conditions of the Erlenmeyer reaction, of a mixture of products consisting of the target oxazolone **119** and 3-*N*-acylcoumarin **120**.[122–124] Evidently this entails the intermediate formation of 2-aryl(alkyl)-4-(2-hydroxybenzylidene)-5-oxazolone **118**. The intramolecular hydrophilic attack by the hydroxy group of the latter on the carbon atom of the carbonyl group leads to the formation of the coumarin **120**. This hypothesis is confirmed by data indicating the formation of



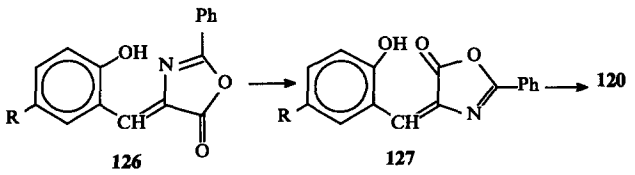
3-benzamidocoumarin **120** (R = C_6H_5, R^1 = H) from 4-(2-acetoxybenzylidene)-2-phenyl-5-oxazolone **119** (R = C_6H_5, R^1 = H)[125] and 4-(2-methoxy-benzylidene)-2-phenyl-5-oxazolone **121**[126] under the conditions involving the removal of the O-protecting groups in these compounds.

The formation of 3-acylaminocoumarins **120** is observed also in the reaction of the saturated oxazolones **122** with salicylaldehyde or its derivatives **123**.[127–129] The course of this reaction is appreciably influenced both by the substituent in the 2-position in the heterocycle **122** and by the substituent R in the second component **123**. According to Kumar and Mukerjee,[127] the use of salicylideneaniline **123** (Y = NC_6H_5) instead of salicylaldehyde leads to a decrease in the yield of acylaminocoumarins **120**. In the case of the oxazolone **122** (R = H), the corresponding coumarin **120** (R = R^1 = H) is obtained only when salicylaldehyde is used. The yield of the coumarin **120** increases in the following sequence of R: H < H < CH_3 < C_6H_5 < C_6H_5CH = CH.

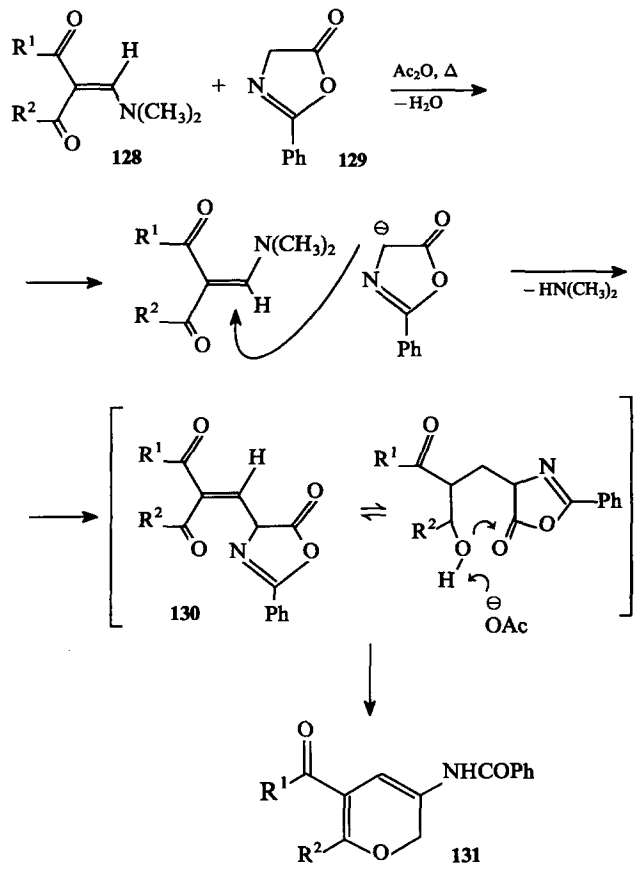
The study of the mechanism of the formation of acylaminocoumarins **120** showed[128] that the process proceeds via the formation of the dihydrocoumarin **125**. In the case of compound **122** (R = H), this intermediate **125** undergoes β-elimination, which leads to the coumarin **120**. In the reaction of 2,4-dimethyl-5-oxazolone **122** (R = R^1 = CH_3) with salicylaldehyde **123** (Y = O) or salicylideneaniline **123** (Y = NC_6H_5), the corresponding hydrocoumarin **125** (Y = O or NC_6H_5) was isolated, since under these conditions the β-elimination of the YH_2 group does not take place.



The acylcoumarins **120** have also been synthesised under the conditions of the photochemical[130] or electrochemical[131] conversion of the *Z*-oxazolone **126** into the *E*-isomer **127**:



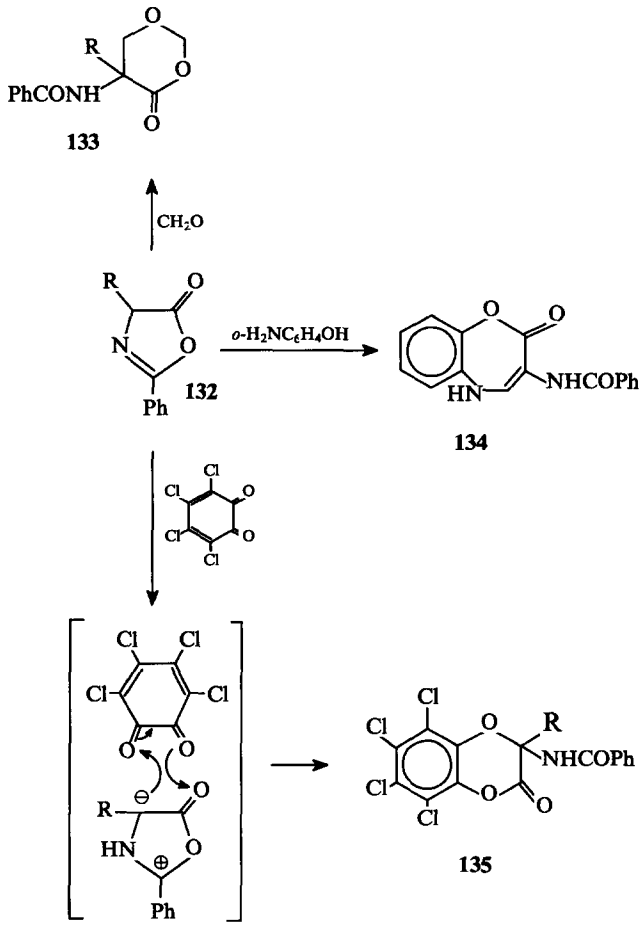
A method for the synthesis of 3-benzamido-2*H*-pyranones **131** via the reaction of esters of 2-acyl-3-dimethylaminoacrylic acids **128** ($R^1 = C_2H_5O$, $R^2 = CH_3$, C_6H_5) or 2-dimethylaminomethylene-1,3-diketones **128** ($R^1 = R^2 = CH_3$, C_6H_5) with 2-phenyl-5-oxazolone **129** has been described:[132]



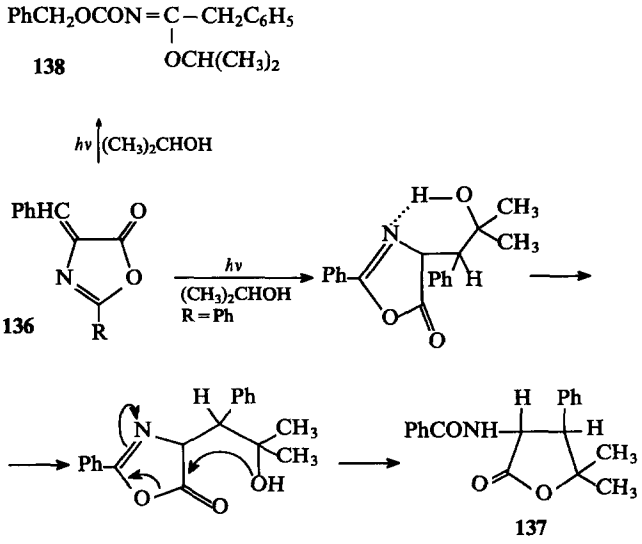
The reaction leads to nucleophilic substitution of the protonated dimethylamino-group in compound **128** and subsequent intramolecular attack by the carbonyl group of the oxazolone **130** on the alcoholic graph of the side substituent, which is completed by cyclisation to the pyran **131**.

The intramolecular opening of the ring in the saturated oxazolone **132** (R = H, alkyl) in the presence of alcohols is observed also in the hydroxymethylation of the heterocycle.[133–135] The reaction products are then 1,3-dioxan-4-ones **133**.

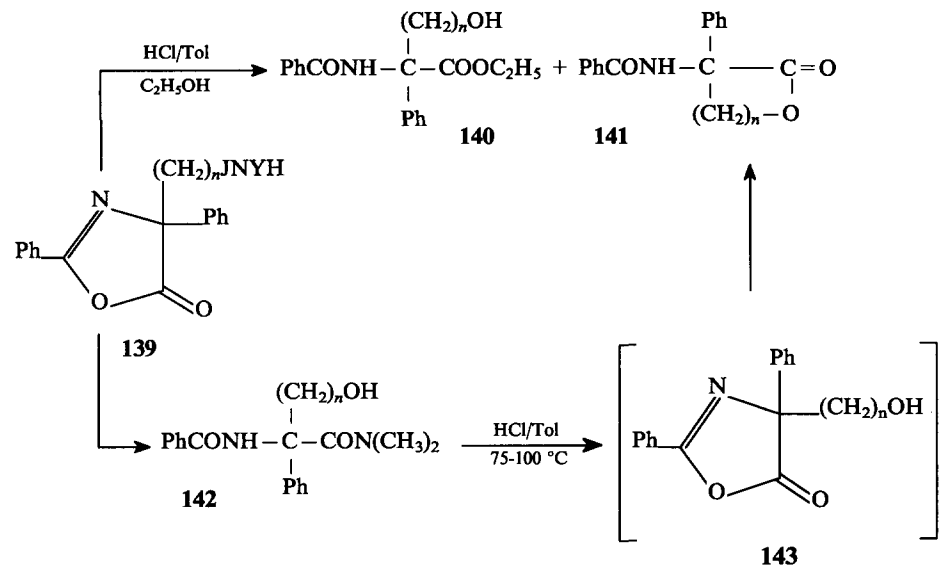
It has been found that the reaction of 4-ethoxycarbonyl-2-phenyl-5-oxazolone **132** (R = $COOC_2H_5$) with *o*-aminophenol leads to the formation of the benzoxazepin **134**,[136] while the reaction of the oxazolone **132** (R = H, alkyl, aryl) with chloranil affords benzodioxanes **135**.[137]



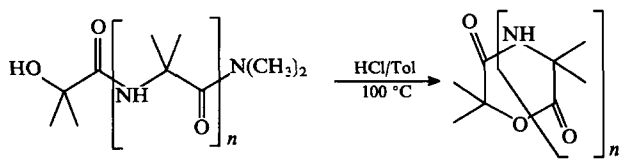
On irradiation with light in solution in 2-propanol, the unsaturated oxazolone **136** (R = C_6H_5) gives rise to the lactone **137** in 17% yield,[138, 139] while 4-benzylidene-2-benzyloxy-5-oxazolone **136** (R = $C_6H_5CH_2O$) affords compound **138** in 92% yield under analogous conditions.[140]



Under the conditions where the O-protecting group is removed from the saturated oxazolone **139** a mixture of the ethyl ester of the *N*-benzamidoacid **140** and the lactone **141** was obtained in the presence of ethanol.[141] It was noted in the same study that the lactonisation can occur when the dimethylamide of the *N*-substituted aminoacid **142** is heated in the presence of hydrogen chloride in toluene (tol.). This reaction proceeds via the intermediate formation of the oxazolone **143**.



Morpholinediones and more bulky cyclic compounds **144** (n = 1 – 4) are formed similarly:[142, 143]



Thus it is readily seen that the study of reactions of 5(4*H*)-oxazolones with oxygen-containing nucleophiles is important for the determination of the chemical properties of these heterocyclic systems and for the synthesis of organic compounds belonging to a wide variety of classes.

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