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Review Article

STUDY ON SYNTHESIS AND DIFFERENT BIOLOGICAL ACTIVITIES OF OXAZOLE BASED DERIVATIVES-A REVIEW

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ABSTRACT

Oxazole based bioactive molecules have played very important role in the field of medicinal chemistry over decades especially as central nervous system depressants, anti-cancer & anti-inflammatory agents. This review is about the different synthetic pathways of oxazole based molecules & their biological activities.

Keywords: Oxazoles, Anti-Convulsants, Anti-Cancer Agents, Anti-Inflammatory Agents.

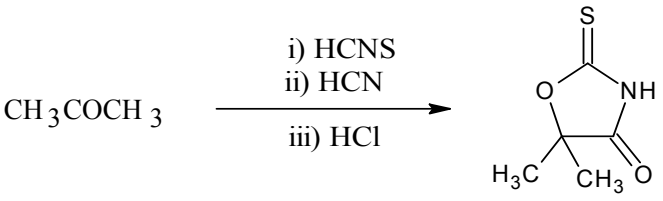
INTRODUCTION

Heterocyclic compounds like polycyclic ring compounds, are usually known by non-systematic names[1]. In the family of heterocyclic compounds nitrogen and oxygen containing heterocyclic are an important class of compounds in the medicinal chemistry and also contributed to the society from biological and industrial point which helps to understand life processes[2]. Oxazole are five member heterocyclic compounds containing in their rings two hetero atoms, one of which is nitrogen and other is oxygen. Standard drugs used in some of the medicinally important derivatives containing oxazole are Trimethadione etc. which possess antiepileptic[3] properties. Oxazolidinones are novel class of antibacterial agents. Linezolid the first and only member of the oxazolidinone class to be approved for clinical use is highly effective against multi-drug resistant Gram-positive bacteria, including staphylococci, streptococci and enterococci. Linezolid has been approved for treating hospital and community acquired pneumonia, skin infections and diabetic foot infections caused by Gram-positive bacterial strains[4,5]. It also showed activity against certain Gram-negative pathogens, particularly those associated with community acquired respiratory tract infections (*Moraxella catarrhalis* and *Haemophilus 16nfluenza*) and some anaerobes[5,6].

Synthesis of Oxazolidine-2,4-diones[7].

Method 1: Oxidation of 2-Thio-4-Oxazolidones:

Acetone, potassium cyanide, and potassium thiocyanate in the presence of concentrated hydrochloric acid give 5,5-dimethyl-2-thio-4-oxazolidone.



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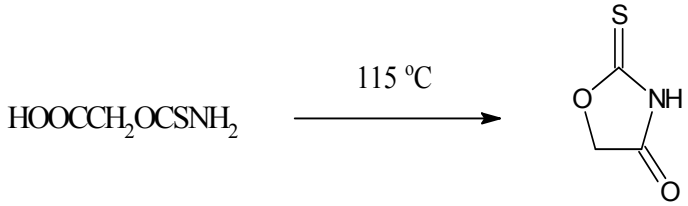
Replacement of acetone by its cyanohydrins and use of ammonium thiocyanate are reported to give a better yield of 5,5-dimethyl-2-thio-4-oxazolidone,but the original method has been improved and gives yields of 62-75%. The reaction has been extended to formaldehyde, acetaldehyde, benzaldehyde and ethyl methyl ketone, but fails with some higher ketones, possibly because of limited solubility of the ketones or intermediate cyanohydrins in the aqueous medium[8]. 2-Thio-4-oxazolidone (90%) was obtained by heating thiocarbamoylglycolic acid at 115°C. for 30 min.



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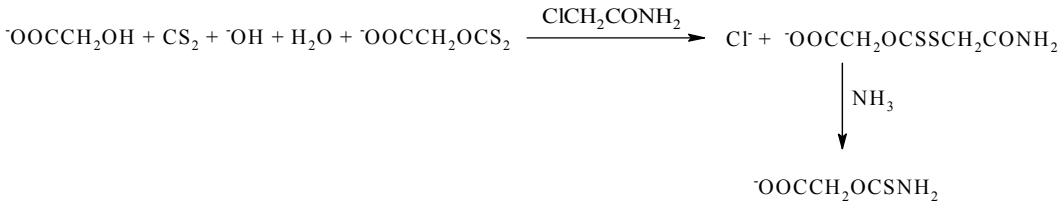
The required acid was obtained indirectly from sodium glycolate.



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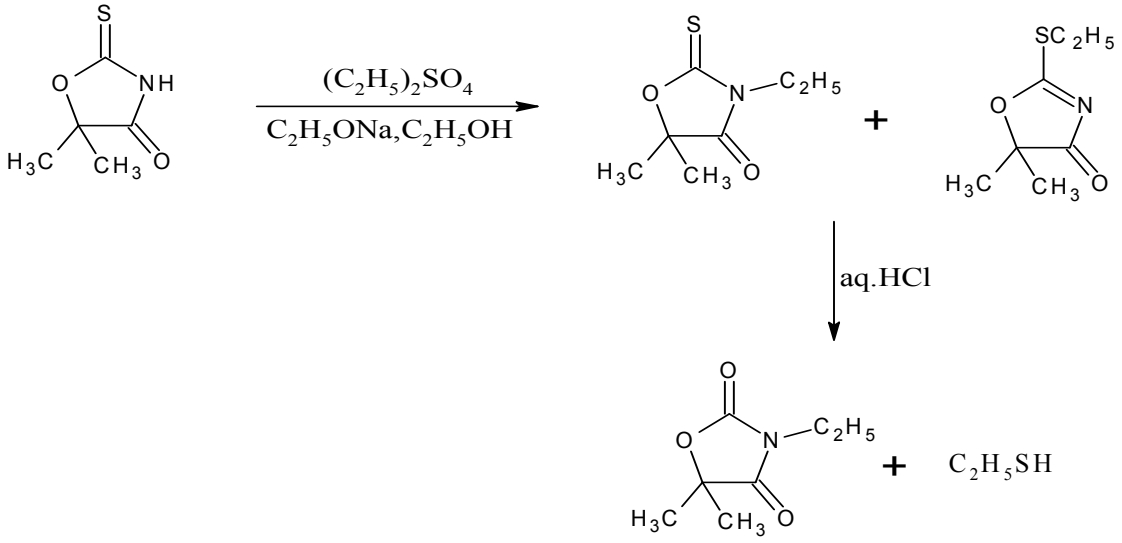
N-Ethylthiocarbamoyl glycolic acid, $C_2H_6NHCSOCH_2COOH$, cyclized so readily that 3 ethyl-2-thio-4-oxazolidone was isolated directly after reaction of ethylamine with the above acetamide intermediate (80%) or with the corresponding acetic acid. 3 Phenyl-2-thio-4-oxazolidone was obtained similarly 3-Alkyl-2-thio-4-oxazolidones are more conveniently prepared by the alkylation[8] of 2-thio-4-oxazolidones; N-alkylation (30-50%) is accompanied by X-alkylation, but the products are easily separated as the 2-alkylthiooxazol-4-ones are readily hydrolyzed by acids to mercaptans and oxazolidine-2,4-diones, which are soluble in aqueous ammonia, e.g.,



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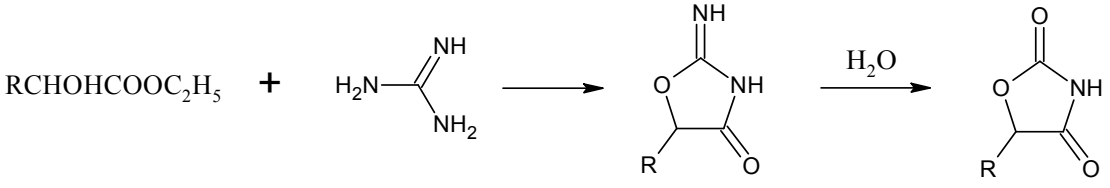
The proportion of *N*-alkylation compared with 8-alkylation decreases with increasing size of the alky group. The *S*-alkyl derivatives are so readily hydrolyzed that oxazolidine-2,4-diones may be formed during alkylation unless conditions are strictly anhydrous, and the products then undergo alkylation to 3-alkyloxazolidine-2,4-diones. 3-Benzyl- and 3-ethyl-5,5-dimethyl-oxazolidine-2,4-dione were obtained in this way from 5,5-dimethyl-2-thio-4-oxazolidone.

Method 2: Hydrolysis of 2-Imino-4-Oxazolidones.

Esters of α-hydroxy acids condense with guanidine (50% solution in ethanol) to yield 2-imino-4-oxazolidones, which are isomeric with hydantoins and are frequently termed pseudohydantoins; the imino compounds are readily hydrolyzed to oxazolidine-2,4-diones (e.g., R = H, CH_3, C_6H_5) .



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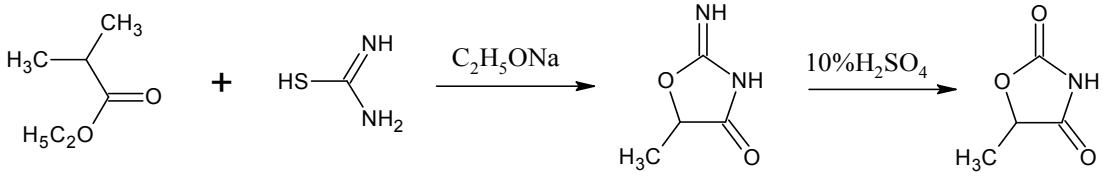
Guanidine can be replaced by its nitrate and one equivalent of sodium ethoxide, or by thiourea with sodium ethoxide as condensing agent, as in the preparation of 2-iminod-methyl- and 2-imino-5-phenyl-4-oxazolidone.



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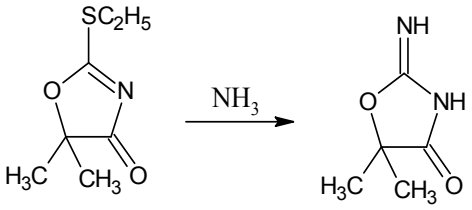
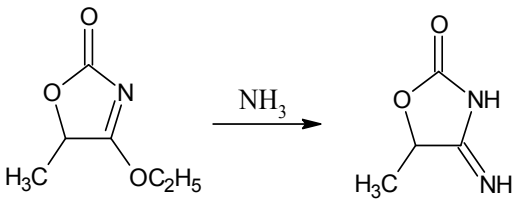
The intermediate 2-imino compounds obtained from thiourea were formerly regarded as α-hydroxyacyl cyanamides, and the oxazolidine-2,4-diones as 1,3-di(α-hydroxyacyl) ureas. The compound obtained from lactide and alcoholic potassium cyanamide is presumably 2-imino-5-methyl- 4-oxazolidone.



2-Imino-5,5-dimethyl-4-oxazolidone has also been prepared by the action of cold aqueous ammonia on 2-ethylthio-5,5-dimethyloxazol-4-one[50], and 4-imino-5,5-dimethyl-2-oxazolidone was obtained by ammonolysis of 4-ethoxy-5,5-dimethyloxazo1-2-one in ethanol. Acid hydrolysis of both imino compounds gave 5,5-dimethy1oxazolidine-2,4-dione[8,9].



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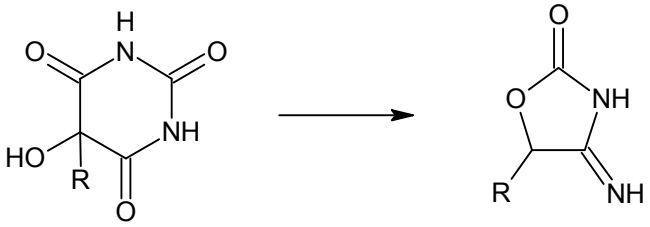
2-Imino-4-oxazolidones are also obtained by the action of alkali on α-bromoureides and 5-bromobarbituric acids, and by the condensation of esters of α-chloro acids with substituted urea, as described below **(method 7)**.

Hydrolysis of 2-imino-4-oxazolidones to oxazolidine-2,4-diones (80% yield) occurs very readily with aqueous mineral acids, e.g., with boiling 10% sulfuric acid for 15-30 min. Alcoholic hydrogen chloride appears less satisfactory than the aqueous acid[9], and 30 % sulfuric acid was used to convert 5,5-diethyl-2-imino-4-oxazolidonien to 5,5-diethy1oxazolidine-2,4-dione. The condensation product obtained from ethyl mandelate and dicyandiamide in the presence of sodium methoxide was hydrolyzed to 5-phenyloxazolidine-2,4-dione with 67% sulfuric acid.

Method 3: Alkaline Hydrolysis of Dialuric acids.

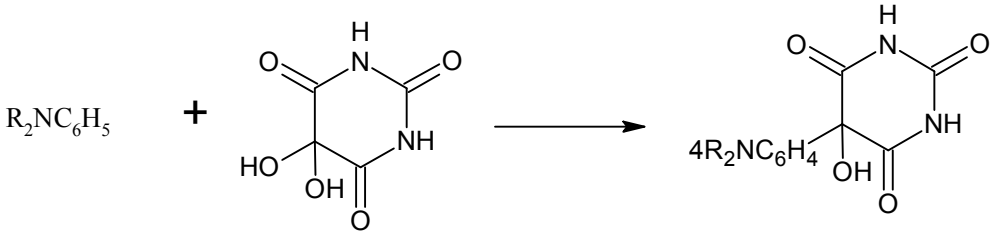
Oxazolidine-2,4-diones[10] are formed from dialuric acids **(I)** by the action of aqueous sodium hydroxide either at room temperature or at 100°C. For 20-30 min. and in many cases (especially when R = aryl) the products **(II)** crystallize from the acidified solutions:



I II

Optimum results are achieved with 2-3 equivalents of alkali and, if less than 2 equivalents is used, fission of the pyrimidine ring occurs but formation of the oxazolidinedione is incomplete. N-Alkyl (or aryl) and N,N'-dialkyl (or diary1) dialuric acids also yield oxazolidinediones**,** but the reaction proceeds most satisfactorily with 5-monosubstituted dialuric acids.

Alloxan hydrate reacts with aromatic amines, such as aniline, methylaniline, and dimethylaniline, to give 5-*p*-aminophenyldialuric acids (R = H or CH_3).



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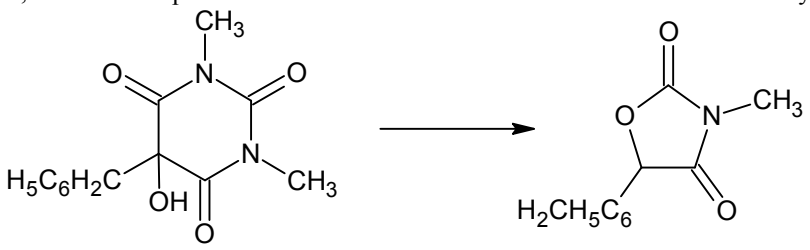
Substitution occurs *para* to the amino group; if this position is occupied, as in *p*-toluidine, reaction usually does not occur, although a pseudocumidine, thought to be 5-amino-l,2,4-trimethylbenzene, gave a dialuric acid in the usual way. Phenols and phenol ethers react similarly with alloxan, which substitutes *para* to an activating group or, if this position is occupied, in the *ortho* position; e.g., *p*-cresol yields 5-(2-hydroxy-5-methyIphenyl) dialuric acid. A considerable number of dialuric acids have been prepared in this way, including a few from heterocyclic compounds and some of the dialuric acids have been converted into oxazolidine-2,4-diones which, however, were described as tartronimides[8-11].

Dialuricacids can also be prepared by the oxidation of & alkyl or 5-arylbarbituric acids with potassium dichromate or with hydrogen peroxide. *N*-Substituted dialuricacids prepared in this way were used to investigate the influence of *N*-substitution on the formation of oxazolidine-2,4-diones.1,5-Dialkyl (or ary1) dialuricacids give 5-alkyl(or

aryl)oxazolidine-2,4-diones and 3-substituted oxazolidinediones were not isolated; any 3-substituted oxazolidine formed by the alternative ring closure would probably be hydrolyzed further, as these compounds are labile in aqueous alcoholic alkali. Alkaline degradation of 5-benzyl-l,3-diniethyldialuric acid gave a low yield of 5-benzyl-3-methyloxazolidine-2,4-dione, and a better yield was obtained when the dialuricacid was merely boiled in aqueous solution.



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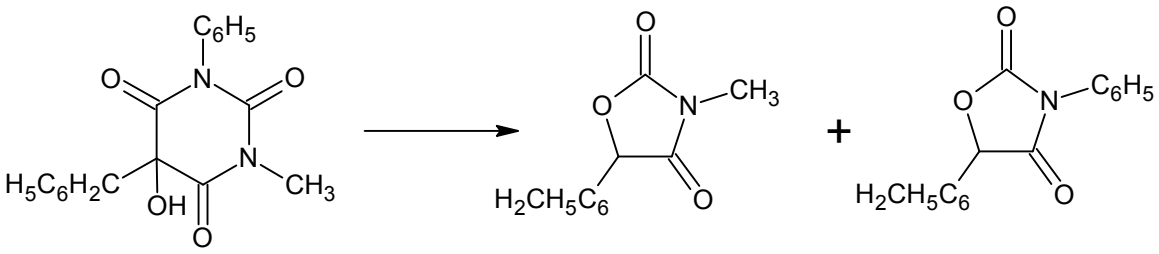
Dialuricacids bearing different *N*-alkyl substituent can lead to mixtures of two oxazolidinediones, but the course of the reaction is not simple.



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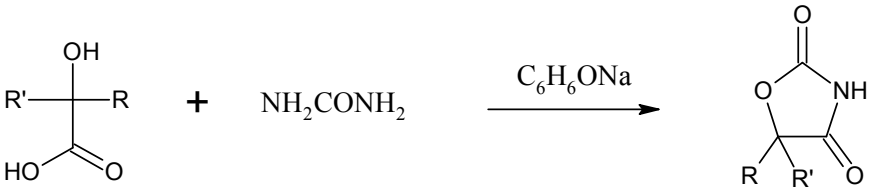
N,N'-Dialkyl-5-bromobarbituric acids yield hydantoins, but other 5-bromobarbituric acids yield oxazolidine-2,4-diones when treated with aqueous alkali. This method is considered together with syntheses from α-bromoacylureas **(method 7)**, since these compounds have been isolated as intermediates in the reaction.

Method 4: Condensation of esters of α-hydroxy acids with Urea.

Esters of α-hydroxy acids condense with urea in the presence of sodium ethoxide to yield sodium salts of oxazolidine-2,4-diones.



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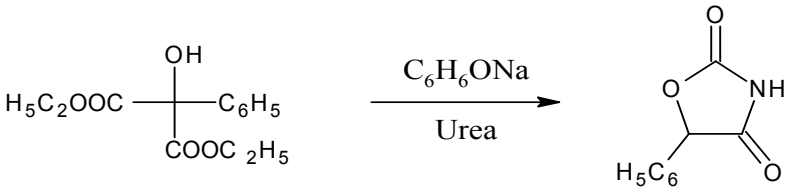
Yields are about 80%, and the reaction has been used extensively since interest has developed in oxazolidine-2,4-diones as medicinal substances. This method is convenient because of the accessibility of the esters and permits the preparation of a wide range of 5-monosubstituted and 5,5-disubstituted oxazolidine-2,4-diones**.** Acetone derivatives of α-hydroxy acids (i.e., 1, 3-dioxolan-4-ones) can be used instead of the alkyl esters, and urea can be replaced by urethanes.

The interaction of urea, esters of α-hydroxy acids, and sodium ethoxide was reported in 1908 to give 1,3-di(α-hydroxyacyl)urea, thirty years elapsed before the products were recognized as oxazolidine-2,4-diones and the yields were improved by using molecular equivalents of reactants[12]. Condensation is usually effected by heating the reactants with one equivalent of alcoholic sodium ethoxide on a steam bath for periods up to 15 hr., and the alcohol is then removed under reduced pressure[12]. The residue of sodium salt (or the solution, after aspiration to remove ammonia) may be *N*-alkylated directly[9], or the oxazolidine-2,4-dione is liberated by acidification with mineral acid, and collected by filtration or by extraction into ether; the product is purified by distillation under reduced pressure or by crystallization.[12] Heating urea with ethyl lactate or ethyl glycolate, without a condensing agent at 175-180°C and in a current of air gives satisfactory yields of 5-methyloxazolidine-2,4-dione and oxazolidine-2,4-dione. The progress of the reaction can be followed by estimation of the ammonia liberated; unchanged urea is then removed as the oxalate or decomposed with the theoretical quantity of nitrous acid before isolation of the product by distillation under reduced pressure.

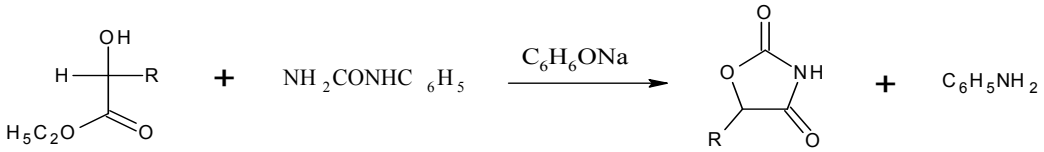
The esters of α-hydroxy acids are usually prepared by esterification of the acids obtained, via the amides, by hydrolysis of aldehyde or ketone cyanohydrins. Some sterically hindered amides resist hydrolysis, but the amides can be converted into 2,4-oxazolidinediones with diethyl carbonate or ethyl chloroformate **(method 5)**. The esters can also be obtained by the interaction of diethyl oxalate and two equivalents of an alkyl magnesium halide. Esters of aryl tartronic acids were found to condense with urea to give products[13] which were later recognized as oxazolidine-2,4-diones[14].



12

Dialuricacids apparently are not formed as intermediates in this reaction, as 5-(2,4-dimethoxyphenyl)dialuricacid is stable and not converted into the oxazolidinedione under similar reaction conditions[15]. This modification of the α-hydroxy ester method has little practical importance because the yields of oxazolidine-2,4-diones are low and the tartronic esters are not easily prepared.

The behavior of three substituted ureas with ethyl mandelate and ethyl α-hydroxybutyrate has been investigated, 5-phenyloxazolidine-2,4-dione (74%) and 5-ethyloxazolidine-2,4-dione (41%) being obtained from phenyl urea.



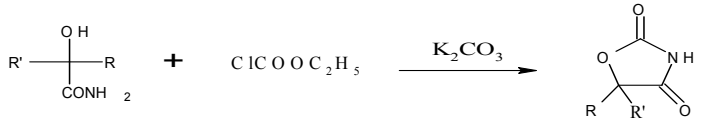
R = C_6H_5 or C_2H_5

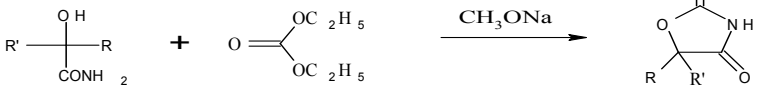
13

1-Acetyl-3-methylurea similarly gave 5-phenyloxazolidine-2,4-dione (42%) from ethyl mandelate, but l-methyl-3-phenylurea did not yield an oxazolidinedione with either ester, so that 3-substituted oxazolidine-2,4-diones cannot be prepared by this method. Anilides and methylamides isolated from these reactions were possibly formed from intermediate 3-phenyl- or 3-methyloxazolidine-2,4-dionesa s well as directly from the esters and aniline or methylamine. Ethyl benxilate and urea gave 5,5-diphenyloxazolidine-2,4-dione (95 %), also obtained in 65 % from l-acetyl-3-methylurea.

Method 5: Condensation of amides of α-hydroxy acids with alkyl carbonates or chloroformates.

Amides of α-hydroxy acids condense with alkyl chloroformates, or with dialkyl carbonates[16] (179), to yield oxazo1idine-24-diones.





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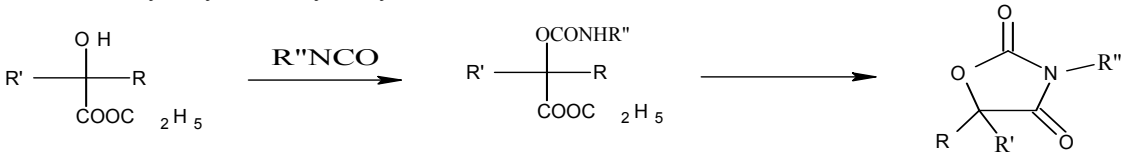
In the former method an alkyl chloroformate is simply heated with the α-hydroxy acid amide or is added slowly to a solution of the amide in an inert solvent (e.g., boiling toluene) containing potassium carbonate.[12] The more widely used condensation of α-hydroxy acid amides with dialkyl carbonates (usually ethyl carbonate) is effected with a sodium, potassium, or magnesium alkoxide[16] under conditions similar to those used for condensing esters with urea (method 4), and optimum yields are obtained with sodium methoxide as condensing agent. The amides of α-hydroxy acids are obtained as intermediates in the hydrolysis of cyanohydrins to α-hydroxy acids,[12] and the dialkyl carbonate-amide method therefore provides a convenient alternative to the ester-urea method for preparing 2,4-oxazolidinedione. It is particularly useful for sterically hindered amides which are difficult to hydrolyze: e.g., 2-hydroxy-2 isopropyl-3-methylbutyramidaen d 2-hydroxy-2,3,3-trimethylbutyramide[16].

Method 6: Cyclization of urethans of α-hydroxyacids and their esters.

Interaction of alkyl or aryl isocyanates and esters of α-hydroxy acids yields the corresponding urethans, which are cyclized to 2,4-oxazolidinediones when heated and in other ways.[17]



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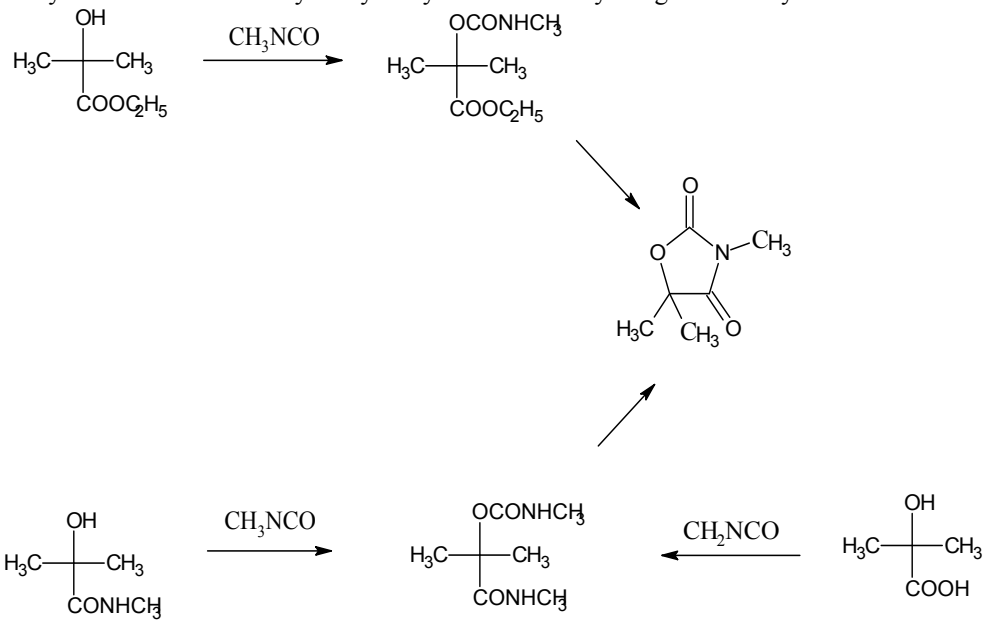
The reaction has been known since 1898 but, apart from its application to the preparation of benzilic acid anilide, has attracted little further attention until recently. The outstanding advantage of this method is that 3-alkyl (or aryl)-2,4-oxazolidinediones are formed directly, the nature of the N-substituent **(R")** depending on the isocyanate component **(R"NCO).** 3-Aryl-2 4-oxazolidinediones are best prepared by this method.

3,5,5-Trimethyl-2,4-oxazolidinedione was obtained by treating ethyl α-hydroxyisobutyrate or *N*-methyl-α-hydroxy-isobutyramide with methyl isocyanate, and cyclizing the intermediate urethans by heating them alone, or with aqueous carbonate, or with sodium in ether. 3,5,5-Trimethyl-2,4-oxazolidinedione (60%) was also obtained from N-propyl-or-(N-methylcarbamoyloxy) isobutyramide, which lost n-propylamine when heated. These methods of preparation avoid difficulties encountered in methylating 5,5-dimethyl-2,4-oxazolidinedione,[18] but the difficulties are mainly due to alkylating in an aqueous medium and are overcome by methylating under anhydrous conditions.



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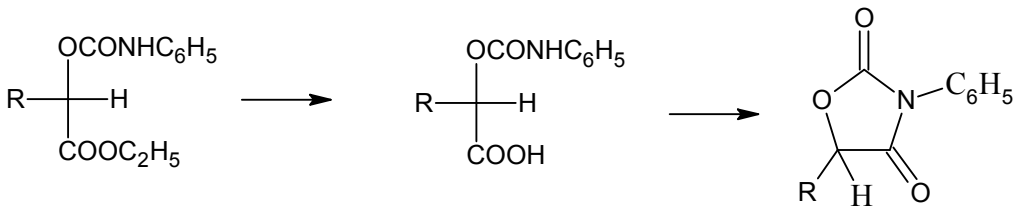
In the original isocyanate method for preparing oxazolidinediones, the esterurethans were hydrolyzed with aqueous alkali and the free acids were heated in aqueous solution, or the esters were merely boiled with water.



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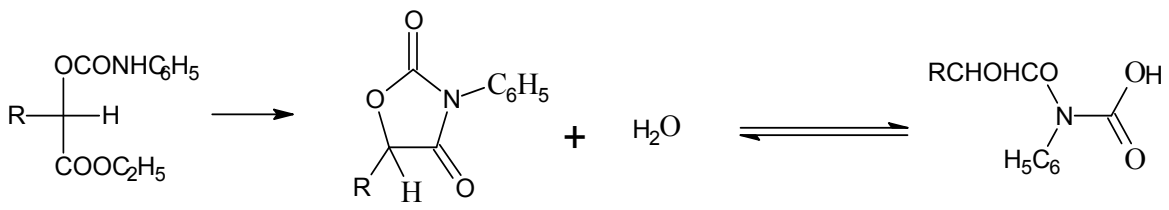
Although the reaction was formulated in this way, the urethans probably cyclize directly, so that the acids obtained with aqueous alkali may have been formed from the oxazolidine-2,4-diones; some of the supposed phenylurethans of α-hydroxy acids are therefore probably carbamic acids.



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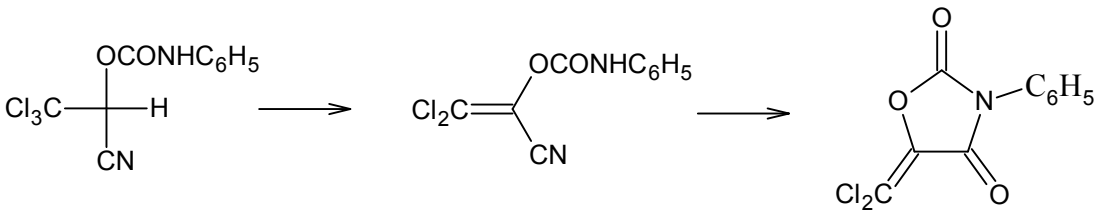
Cyclizations were later affected by heating the urethans alone or with sodium in ether ring closure with sodium ethoxide have apparently not been tried.

The phenylurethan derivative of chloral cyanohydrin loses hydrogen chloride when treated with alkali, and heating the product with acids yields 5-dichloromethylene-3-phenyloxazolidine-2,4-dione[17] and not the supposed 5-dichloromethyl compound.



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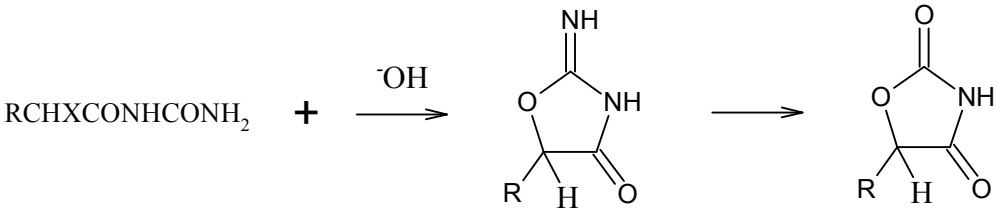
The dichloromethyleneoxazolidine-2,4-dione was also obtained by heating chloral cyanohydrin phenylurethan with concentrated HCl in a sealed tube, and by heating ethyl trichloroacetate phenylurethan with aqueous alkali.

Method 7: Preparation from esters of α-halogen acids and from α-halogenoureides or 5-bromobarbituric acids.

Alkali induces cyclization of α-halogenoureides to 2-imino (or substitutednimino)-4-oxazolidones (pseudohydantoins), which can be isolated or converted into oxazolidine-2,4diones**.**



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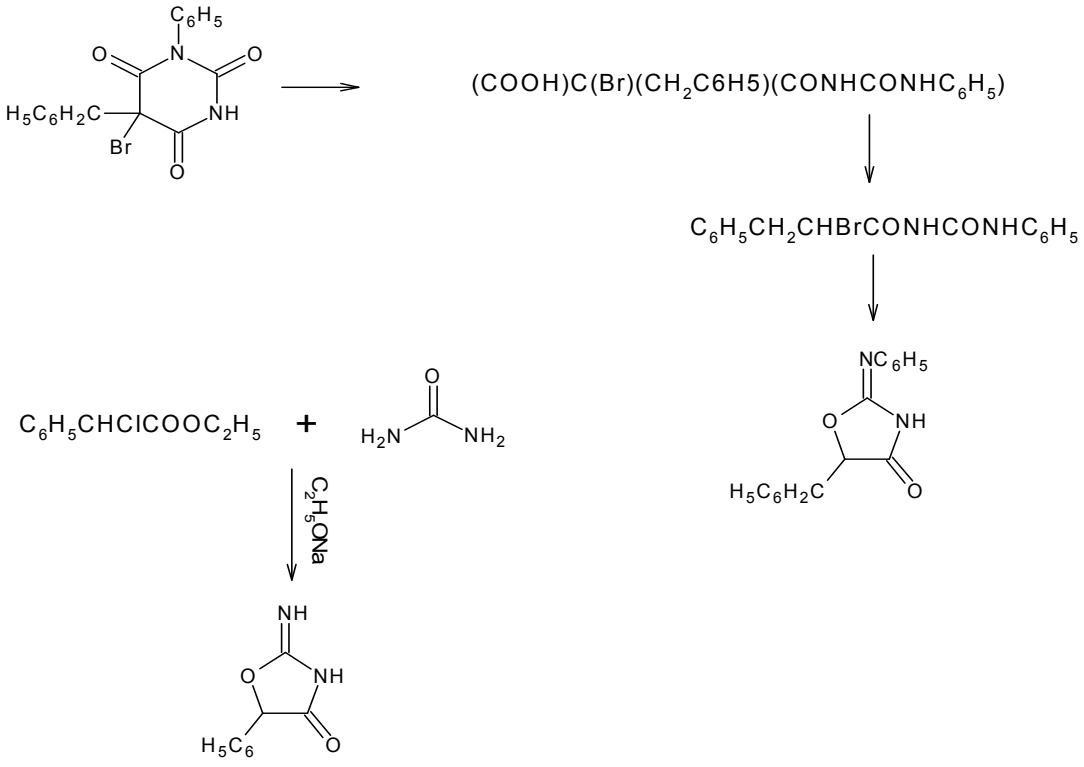
5-Bromobarbituric acids when treated with aqueous alkali give bromoureides as intermediates in this conversion, and the condensation of esters of α-halogen acids with urea (or substituted urea) leads to 2-imino-4-oxazolidones, presumably via the chloroureides.



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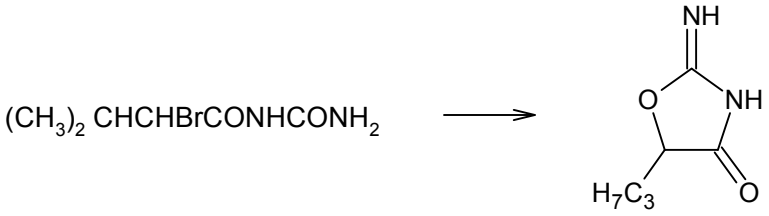
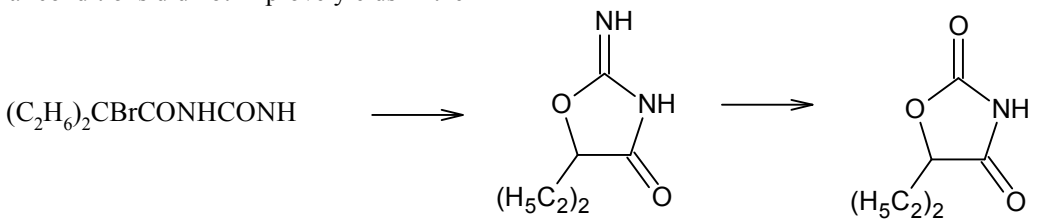
The 2-alkyl(or aryl)imino-4-oxazolidones are converted satisfactorily into 2,4-oxazolidinediones by acid hydrolysis, but the overall yield of a 2,4-oxazolidinedione by this method is usually poor because of inefficiency in the initial cyclization. The imino compounds are also hydrolyzed by alkali, although more slowly, so that a small proportion of 2,4-oxazolidinedione is formed directly.

Dehydrobromination of bromural (α-bromoisovalerylurea) with alcoholic potassium hydroxide gives a 45% yield of 2-imino-5-isopropyl-4-oxazolidone, formerly regarded as dimethylacryloylurea.



22

The same product was obtained from the iodoureide. The yield was increased to 65% when the bromoureide was boiled with aqueous ammonium. Carbonate instead of potassium hydroxide, but similar conditions did not improve yields in the cyclization of *N*″-alkyl- or *N*′-arylbromoacylureas. *α*-Bromo-ethylbutyrylurea gave 5,5-diethyl-4-oxazolidone when treated with alkali .



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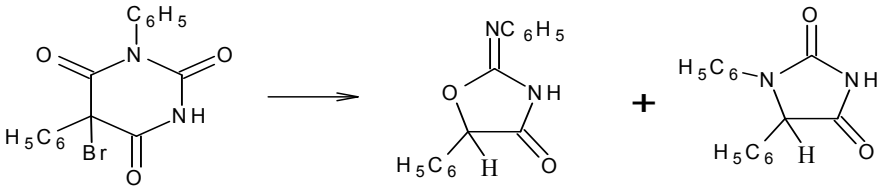
If this change occurs also under physiological conditions, as seems possible, the sedative properties of these bromoureides may be due to the pseudohydantoins or oxazolidinediones so formed.

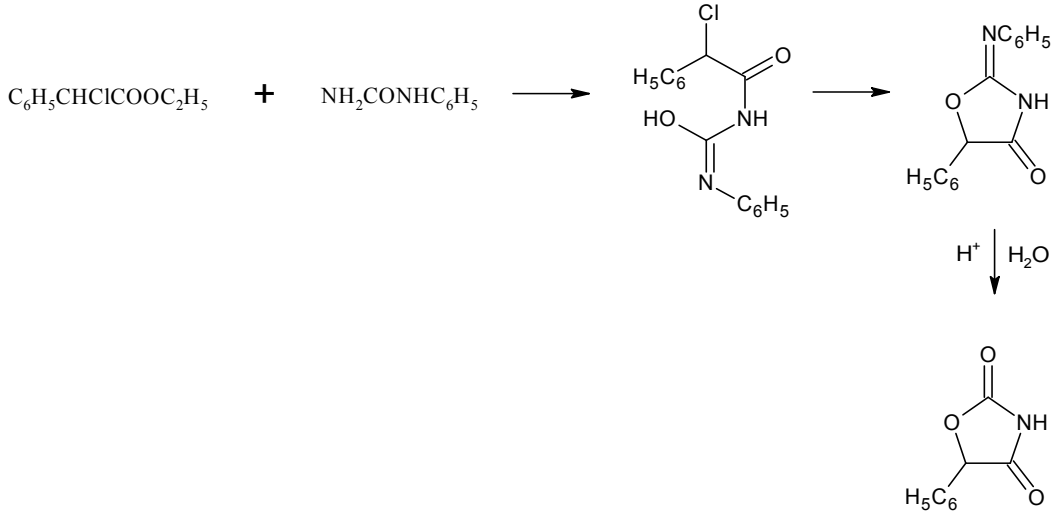
Boiling aqueous or alcoholic alkali converts 5-bromo-1-phenylbarbituric acids into mixtures of 2-phenylimino-4-oxazolidones (pseudohydantoins) and l-phenylhydantoins, in which the former predominate:



24

The preferential cyclization to oxazolidone derivatives accounts for the very poor yields of hydantoins in this type of reaction.[19] 1,3-Disubstituted bromobarbituric acids under similar conditions, however, yield only the hydantoin, or mixtures of two hydantoins if the 1,3substituents are different. The liability of 3-substituted oxazolidine-2,4-diones under alkaline conditions, and the isolation of anilides or methyl amides of α-hydroxy acids from some of these reaction mixtures, suggest that any 3-substituted derivative which is formed is subsequently decomposed.

The reaction of esters of α-chloro acids with urea and substituted ureas yields 2-imino-4-oxazolidones, together with minor quantities of oxazolidine-2,4-diones formed by alkaline hydrolysis of the 2-imino compounds. Reaction presumably proceeds by cyclization of an intermediate α-chloroacylurea in the enolic form.



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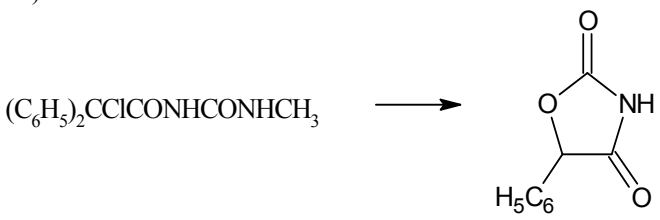
1-Diphenylchloroacetyl-3-methylurea was converted into 5,5-diphenyloxazolidine-2,4-dione (91 %) when heated with pyridine in benzene[20].



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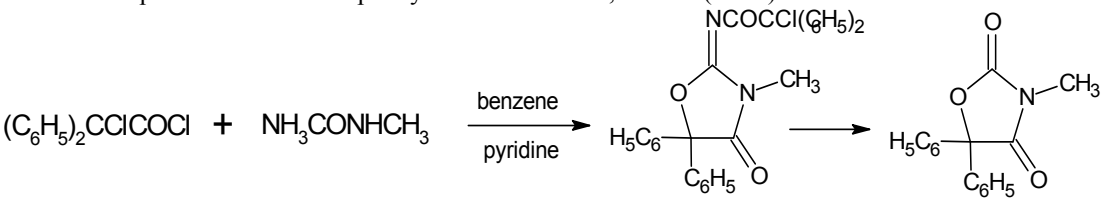
Heating the chloro acid chloride with methylurea in benzene gave only 12.5% of the same oxazolidinedione, but in benzene containing pyridine the product was 2-diphenylchloro acetylimino-3-methyl-5,5-diphenyl-4-oxazolidone (22 %), which on hydrolysis gave 3-methyl-5,5-diphenyloxazolidine-2,4-dione (72 %)[20].



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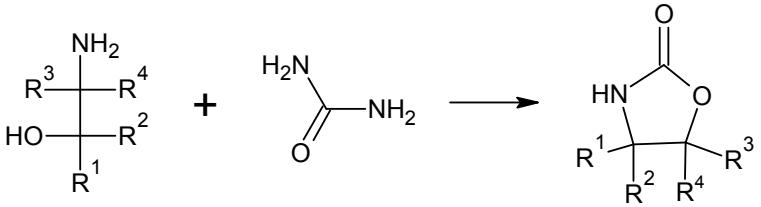
Acid chlorides with alkyl (or aryl) urea normally yield l-acyl-3-alkyl(or aryl)ureas and addition of pyridine to the above reaction mixture apparently induced acylation of both nitrogen atoms[20].

B) Synthesis of Oxazolone derivative.

1. **Synrheasis in mild condition**. Ethanolamine derivative **(2mmol)** and urea **(2mmol)** were mixed in 25 ml pyrex beaker. A few drops of nitromethane were then added. The resulting paste was irradiated in a microwave oven **(λ=12.2, for 5.5 to 3 min)**. The resulting crude products were purified by recrystallisation from $CHCl_3$-EtOH[21].



R^1 = H, Me, Ph, p-ClPh.

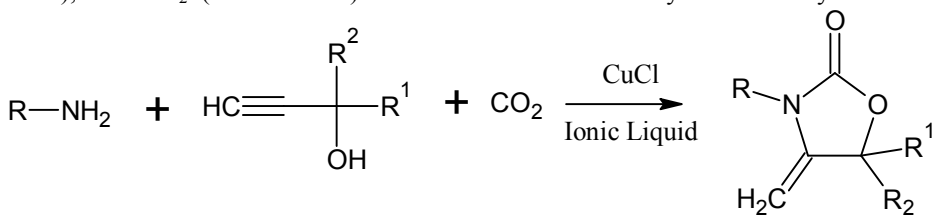
R^2 = H, Me, H, H.

R^3 = H, H, H, H.

R^4 = H, H, H, H.

28

2. **Synthesis of 5-Methylene-1,3-oxazolidin-2-ones .** All reactions were conducted in a 100-mL autoclave with glass tube inside equipped with magnetic stirring. In each reaction, ionic liquid, 3 mL, propargylic alcohol (10 mmol), amine (10 mmol), catalyst (0.2 mmol), and CO_2 (1.5-2.5 MPa) were successively introduced and reacted at 100 °C for the desired period. The resulting mixture (cool) was extracted with diethyl ether (4 mL). Then, the combined organic phase was evaporated and dried in a vacuum to afford the primary product. Recrystallization by water and ethanol[22].



29

3. **(R)-3-(3-Fluorophenyl)-2-oxo-5-oxazolidinylmethanol** (3) To a solution of N carbobenzyloxy-3-fluoroaniline 2 in THF added slowly n-butyllithium in n-hexane under nitrogen condition. After 10 min, (R)-(_)-glycidyl butylate was slowly added. The mixture was stirred for 2 h and stirred at room temperature for 24 h. After completion of the reaction, an aqueous saturated ammonium chloride solution was added and the mixturewas extracted with EtOAc. The organic layer

was washed with brine, dried over anhydrous MgSO4 and concentrated in vacuo. The crude product was recrystallized from EtOAc and n-hexane[23].

4. **General procedure for the long chain alkylcarbonyloxazolidinones.** A solution of the 5-((1H-1,2,3-triazol-1-yl)methyl)-3- (3-fluoro-4-(piperazinium-1-yl) phenyl)oxazolidin-2-one trifluoroacetic acid salt in acetonitrile cooled and treated with triethylamine and an appropriate long chain alkylcarbonyl chloride and stirred to room temp. Dichloromethane was added to the reaction mixture and the solution was washed with water .The organic layer was washed with brine, dried (anhydrous Na_2SO_4), filtered and concentrated to give a solid, which was triturated with ether to give crude solid[24].

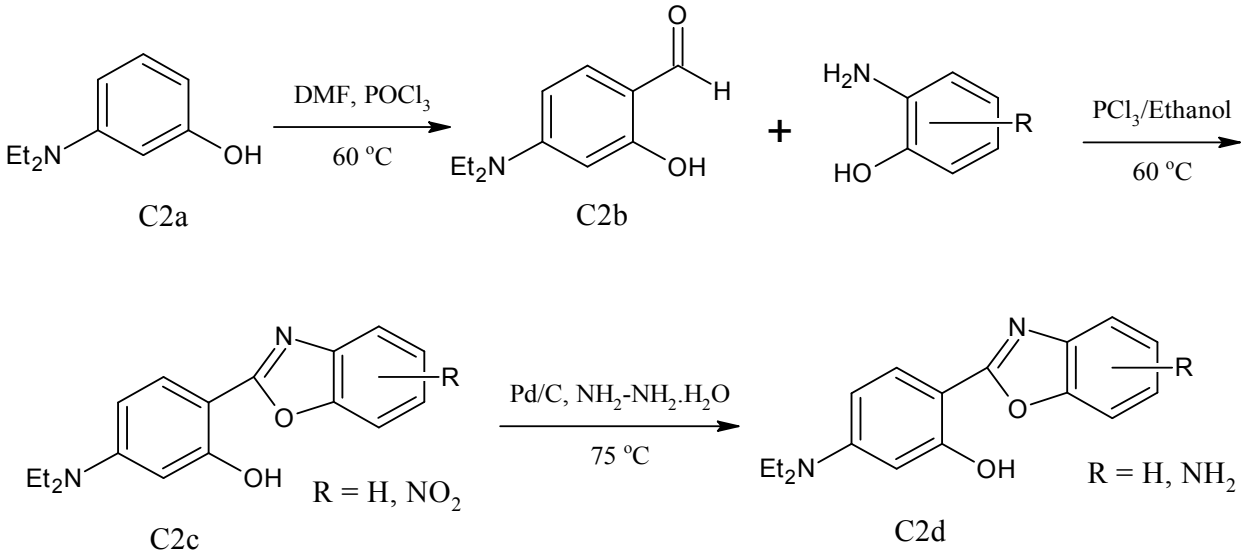
C) Synthesis of benzoxazole derivative.

1. **General procedure for synthesis of 2-substitude benzoxazole (C2d).** Phosphorus trichloride **(0.33 mol)** was added drop wise to a solution of the *p-N,N*-diethyl salicylaldehyde **(C2b) (0.33 mol)** and substituted *o*-aminophenol **(0.33 mol)** in ethanol **(50 mL)**, maintaining the temperature at 40–45°C, The mixture was heated at 60°C for 4 h, after completion of reaction (monitored by TLC) cooled the reaction mass at room temperature and brought the alkaline to pH 8 with aqueous sodium bicarbonate solution (20% w/v). Separated product was collected by filtration and crystallized from isopropyl alcohol[25].
2. **Synthesis of bis(benzoxazoles).**

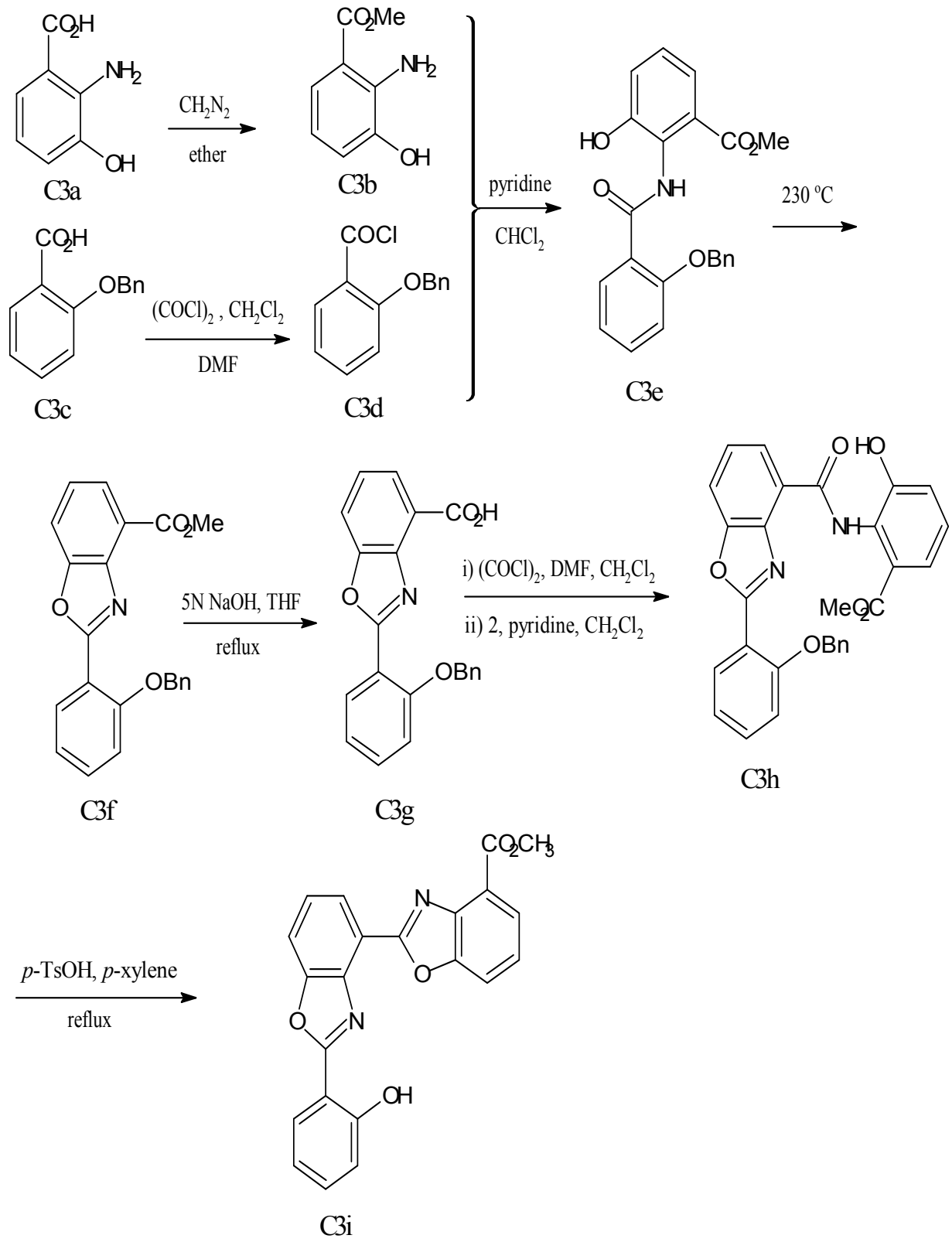
I. **Synthesis of methyl 2-[2-(benzyloxy)phenyl]-1,3-benzoxazole-4-carboxylate (C3f).** Compound **C3e (0.3 mmol)** was heated up to 230 °C under vacuum (ca.40 torr) for 5 h, and purified by flash column chromatography using silica gel as the stationary phase and using ethyl acetate/hexane (1:49, 1:19) as the mobile phase.[26]

II. **Synthesis of methyl 2'-(2-hydroxyphenyl)-2,4'-bi-1,3-benzoxazole-4-carboxylate (C3i).** A solution of compound**C3h (0.1 mmol)** and p-toluenesulfonic acid **(0.3 mmol)** in anhydrous p-xylene **(2 mL)** was refluxed for 2 h, and the reaction was quenched by adding saturated sodium bicarbonate solution. The aqueous phase was extracted with ethyl acetate, and the extract was dried over anhydrous magnesium sulfate. After filtration and concentration, the residue was purified by flash column chromatography using silica gel as the stationary phase and using ethyl acetate/hexane (1:19, 1:9) as the mobile phase[26].

3. **Synthesis of benzoxazole-2-methylenebis phosphonates C4(c-h) & C4 (i-k).** A solution of 4.2 mmol of tetraethyl methylenebiphosphonate, **C4b** in 10 mL of absolute ethanol containing 9.12 mmol sodium(Na) was stirred at 0°C for about 0.5 h. A solution of 3.8 mmol of the Schiffbase **C4a** in 10 mL of EtOH was then added with catalytic amount of 2,3-dichloro-5,6-dicyano-benzoquinone (DDQ) in one portion, and the reaction was stirred at r.t., for ≈ 12 h (TLC). The product mixture was cooled, poured into ice-water, and acidified with conc HCl to pH ≈ 6, followed by extraction with AcOEt (3×50 mL), and the combined organic phase was dried over *anh*. Na_2SO_4 **C4(c-h)**. Bisphosphonate **C4(c,d)** (0.5 g) was dissolved in 15 mL of conc HCl, and the mixture was heated under reflux for ≈ 8h (TLC). After concentrating the product mixture, the crude material was diluted with AcOEt and water. The aqueous layer was evaporated to dryness **C4 (i-k)**[27].



Synthesis of 2-substituted benzoxazole.



Synthesis of bis(benzoxazoles).

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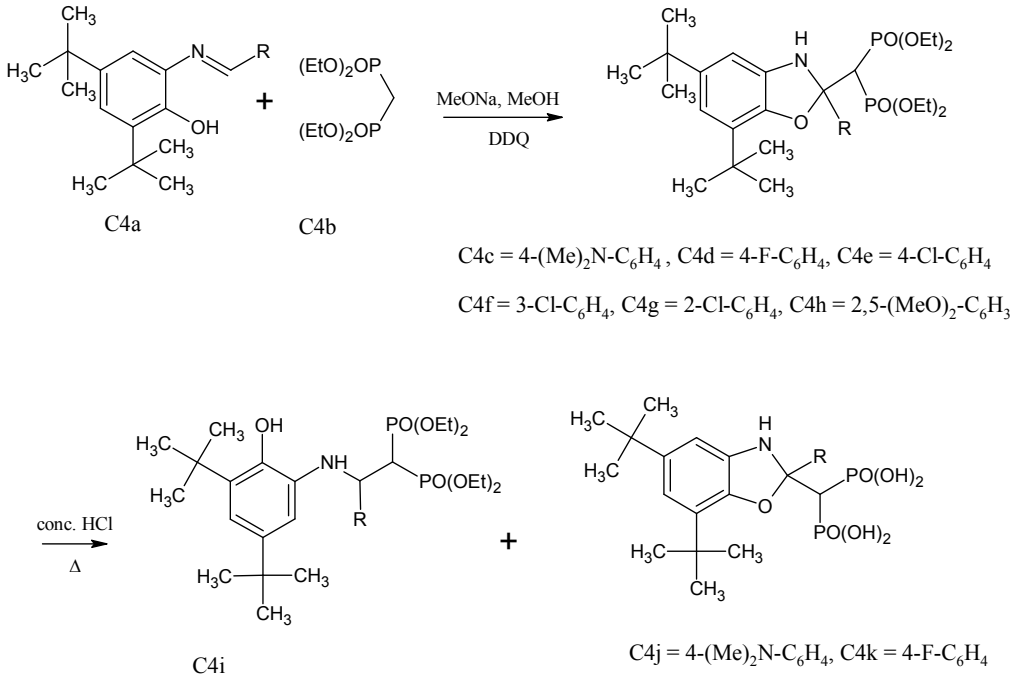

C4a C4b

C4c = 4-$(Me)_2$N-C_6H_4 , C4d = 4-F-C_6H_4, C4e = 4-Cl-C_6H_4

C4f = 3-Cl-C_6H_4, C4g = 2-Cl-C_6H_4, C4h = 2,5-$(MeO)_2$-C_6H_3

C4i

C4j = 4-$(Me)_2$N-C_6H_4, C4k = 4-F-C_6H_4

Synthesis of benzoxazole-2-methylenebisphosphonates.

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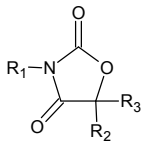
BIOLOGICAL ACTIVITY:



1

Table 1: Anticonvulsant Activity

Compound No.	R_1	R_2	R_3	Comment
1a	*n*-C_3H_7	H	H	Protect against Metrazole & electroshock induced seizures.
1b	*i*-C_5H_{11}	H	H	Protect against electroshock induced seizure. Symptom of Ataxia is minimal among 1a & 1c.
1c	CH_3	H	C_2H_5	Protect against Metrazole induced seizures.
1d	*s*-C_5H_{11}	CH_3	CH_3	Cause CNS excitation. No protection against any type of seizures.

Spielman MA. *et. al.,*[28]

Table 2: Anticancer Activity

Compound No.	Biological activity
C3h	Less potent than C3i against the A-549 and HeLa cancer cells lines.
C3i	Exhibits potent cytotoxic activity against the A-549 and HeLa cancer cells lines. This compound has ability to form metal ion complexes that can bind to DNA[29,30] and inhibit DNA-processing enzymes,[29] research indicate that Mg^{2+} ion binding by **C3i** may lead to biologically relevant complexes with a specific target in cancer cells.
C4c	Active against breast (especially MDA-MB-231/ATCC and BT-549), and prostate carcinoma cell lines (PC-3 and DU-145). Presence of dialkylamino group as a substituent to the aryl-moiety is usually associated with the enhancement in antitumor properties.
C4e	Same activity and SAR profile as C4c.

Table 3: Anti-Inflammatory Activity.

Compound No.	Biological activity
C4c	Presence of the bisphosphonate moiety in **C4(c-k)** is an essential factor in developing the total pharmacological properties for these compounds. Most active structures for chronic inflammation. Presence of the free or alkylatedamino group highly enhanced the efficacy of the compound.
C4d	Posses approximately same activity profile as **C4c**.
C4e	Significantly inhibited the granuloma in a dose-dependent manner.
C4f	Significantly inhibited the granuloma in a dose-dependent manner.
C4g	Significantly inhibited the granuloma in a dose-dependent manner.
C4h	Introducing the two methoxy groups at the phenyl moiety results incomplete loss of the activity.
C4k	Presence of the free or alkylatedamino group highly enhanced the efficacy of the compound.

CONCLUSION

This review gives an idea about the different synthetic pathways of oxazole based molecules & their biological activities and hence it can be a good source for future researcher to develop new potent bioactive oxazole derivatives.

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