STUDIES ON AZLACTONES DERIVATIVES

A THESIS

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(Ph. D.)

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الله

بسم الله الرحمن الرحيم

وقل اعملوا فسيرى الله عملكم ورسوله والمؤمنون

صدق الله العظيم

بسم الله الرحمن الرحيم

STUDIES ON AZLACTONES DERIVATIVES

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ARABIC SUMMARY

SUMMARY

SUMMARY

4-(Tetrasubstituted)-phthalidene or arylidene-2-aryl-5(4)-oxazolones(I and XV) were prepared. Hydrazinolysis of I and XV with hydrazine hydrate and/or phenylhydrazine in ethanol gave the corresponding tetrasubstituted phthalidene hippuric acid hydrazide derivatives (IIa,b and IIIa-c) and α-aryl amido cinnamic acid hydrazides (XVIa-d) respectively. On the other hand, the phenylhydrazide (XVIC) was readily cyclized with acetic acid and sodium acetate to give the corresponding triazine (XVII). Compound (XVII) was obtained by interaction of oxazolone (XVa) with phenylhydrazine in the presence of acetic acid and sodium acetate.

The oxazolone (Ia) reacted with aniline in molar ratio (1:1) or (1:2) and yielded tetrachlorophthalidene N-phenyl hippuric acid amide (IV) and (V), 4-(tetrachloro-2-phenyl carbamoyl)-1,2-diphenyl-5-imidazolone (VI) respectively.

Aminolysis of oxazolones (XVa-f) with primary amines and/or secondary amines in ethanol gave the corresponding α-aryl carbamido-β-aryl acrylamides (XVIIIa-m and XXIa-b).

On the other hand (XVa, XVd and XVf) condensed with m-toluidine or ammonium acetate in the presence of

acetic acid and sodium acetate to give the corresponding imidazolones (XX and XXIIa-c) respectively.

Azidolysis of oxazolones (XVa) with aqueous sodium azide in boiling acetic acid gave α-[tetrazolyl-(1)-5-phenyl -β-(2-naphthyl)]acrylic acid (XXIV).

Oxazolones (XVa,c and d) reacted with aminobenzoic acids to give α-arylcarbamido-β- aryl acryl amide (XXVa-e).

Compounds (XXVa,c and d) underwent ring closure with warming acetic anhydride to give 2-[(α-arylamido-β-aryl) vinyl] (4H)-3,1-benzoxazin-4-ones (XXVIa-c) respectively.

The behaviour of (XXVIb) towards hydrazine hydrate, phenylhydrazine and benzylamine to give the hydrazide derivatives (XXVIIa-b) and (XXIX) has been described.

Similary (XVF) reacted with aliphatic amino acids namely glycine and glutamic acid in aqueous pyridine solution to give the corresponding acrylamides (XXXa-b).

The acrylamide (XXXa) underwent condensation with aromatic aldehydes namely benzaldehyde and/or p-nitrobenzaldehyde in the presence of acetic anhydride and sodium acetate to give the corresponding oxazolones (XXXIa and b). Also when (XXXb) was treated with sodium acetate and acetic anhydride ring closure took place and yielded the oxazolone (XXXII).

Oxazolones (Ia,b) underwent ring opening reaction with cumene under Friedel Crafts condition at room temperature to give the corresponding phthalide derivative (XI).

Similarly the oxazolone (XVa) reacted with m-xylene and/or p-xylene in the presence of anhydrous aluminium chloride and yielded α-benzoylamino-2-naphthylidene-2,4-(or 2,5)-dimethyl acetophenone (XXXIIIa-b).

On the other hand heteroring opening followed by dearylation was found in arylation of oxazolones (Ia and c) under Friedel Crafts condition with o-xylene. Thus, arylation of (Ia and c) by o-xylene gave ω-benzoylamino-3,4-dimethyl acetophenone (XII). Hetero ring opening with 1,4-arylation of oxazolone (Ic) by m-xylene under Friedel Crafts condition was occurred to give (XIV). The hetero-ring fission with replacement of one aryl group by another was observed. Thus, arylation of oxazolone (XVa) with o-xylene yielded deoxybenzoin derivative (XXXIV). The heteroring opening of the oxazolone (XVF) with Grignard reagents namely phenyl magnesium bromide or ethylmagnesium bromide gave (XXXVa-b). The structure assigned to the products was established either from their independent synthesis; their spectroscopically data (IR, n.m.r.) or the both.

GENERAL PART

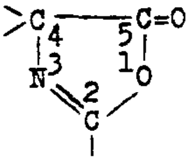
CHEMISTRY OF OXAZOLONES

SYNTHESIS AND CHEMICAL REACTIONS OF 5(4)-OXAZOLONES

OXAZOLONES

Introduction:

Oxazolones are of five possible types, the most important of these are the 5(4)-oxazolones, the 5(2)-oxazolones are recently discovered and are represented by few compounds, few examples of the 2(3)-oxazolones are known, there is one doubtful example of the 4(5)-oxazolones and no 2(5)-oxazolones are yet discovered.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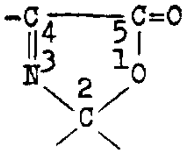
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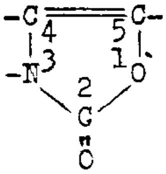
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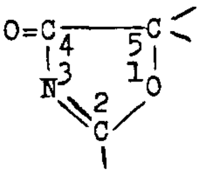
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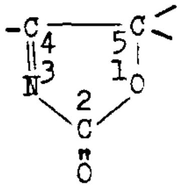
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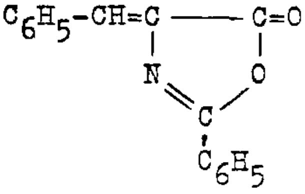
Erlenmeyer[1] proposed the general formula of oxazolones (I) and called it the azlactone of

α-banzamidocinnamic acid. He has prepared other 4-alkylidene-5(4)-oxazolones.

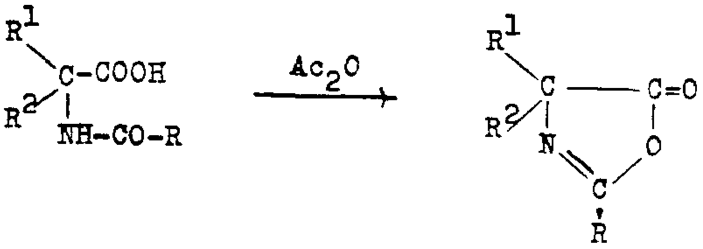


(I)

Synthesis:

1) **From α-acylamino acids:**

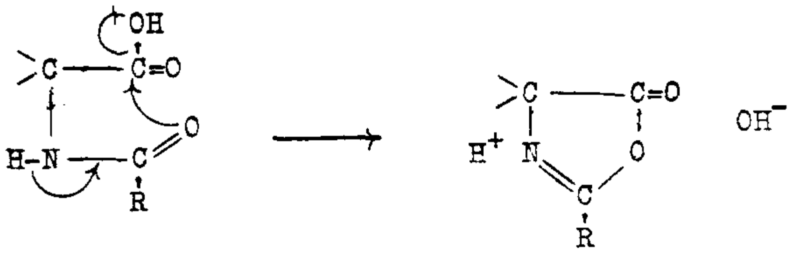
Pyrolysis of α-benzamidocinnamic acid as reported by Erlenmeyer[2], gives 2-phenyl-4-benzylidene-5(4)-oxazolones. However, oxazolones (II) are prepared generally by dehydration of α-acylamino acids (III) with an acid chloride[3] in the presence of pyridine or acid anhydride[4] (as acetic anhydride) to give the corresponding product.



(III) (II)

	R	R^1	R^2	Ref.
a,	C_6H_5	H	H	5,6
b,	C_6H_5	CH_3	H	7
c,	$4-NO_2.C_6H_4$	C_4H_9	H	7
d,	CH_3	$C_6H_5.CH_2$	H	7
e,	C_6H_5	H	C_6H_5	8
f,	CH_3	$2-Cl.C_6H_4$	$3,4-(OCH_3)_2C_6H_3$	9
g,	$2-OH-C_6H_4$	H	H	10
h,	$2-OH-C_6H_4$	H	CH_3	10
i,	$2-OH-C_6H_4$	H	C_3H_7	10
j,	$2-OH-C_6H_4$	H	C_4H_9	10
k,	$2-OH-C_6H_4$	H	$CH_2C_6H_5$	10
l,	$2-OH-C_6H_4$	H	CH_2COOH	10
m,	$2-OH-C_6H_4$	H	CH_2CH_2COOH	10

The formation of oxazolones from α-acylamino acids has uncertain mechanism since it is not known which oxygen atom is lost from the acid during cyclization. It seems, however that the reagents which affect the oxazolone formation are those which react more readily with a carboxyl than with an amido group and therefore, the carboxyl carbon is attacked by the negative end of the amide dipole and the removal of the hydroxyl group being facilitated by the reagent.



It was reported[11], that the second order rate constants for the carboimide cyclization of α-acylamino acids (III) to give the oxazolones (II) were not affected by the electronic nature of the N-acyl substituent.

However, the rates of cyclization of (III) ($R = C_6H_5$, $R^1 = H$) increased in the order R^2 = hydrogen, methyl, ethyl, butyl, benzyl due to increased of steric size of R^2 and subsequent increased of the conformational population necessary for cyclization.

DL-amino acids were reacted with chloroacetyl chloride[12] and tetrafluoropropionic anhydride[13] and yielded (IV) and (V).