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Synthesis of New Oxazolin-5-ones Derivatives as Antibacterial Agents

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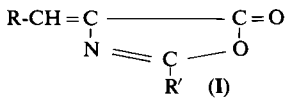
Abstract □ 1-Aryl-4-arylidene-2-oxazoline-5-ones (**I**) and the corresponding unsaturated amidoesters (**II**) and arylidene hypuric acid hydrazide (**III**) were obtained. The hydrazides and 1-aryl-1,3-dithiophenol-2-amidopropan-3-ones derivatives (**IV**) were also obtained. The derivatives were tested for their antibacterial activities.

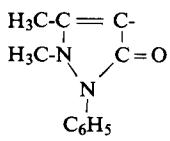
Keywords □ 1-aryl-4-arylidene-2-oxazoline-3-ones, aryl-1,3-dithiophenol-2-aminopropan-z-ones, bacterial effect.

CHEMISTRY

The antibacterial and antitubercular activity of oxazolone derivatives in many active drugs[1-3] led many investigators to synthesize new compounds containing oxazolinone ring. 1-Aryl-4-arylidene-2-oxazoline-5-ones (**I**) were readily obtained by condensation of aroylglycines with different aldehydes in acetic acid/sodium acetate.



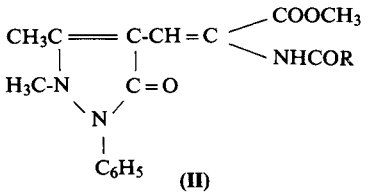
(**I**)

I	R	R′
a		C_6H_4Cl *p*
b	"	"	C_6H_5
c	"	"	$C_6H_5CH_2$
d	"	"	$C_6H_4{\cdot}CH_3O$ *p*
e	$C_6H_4{\cdot}CH_3O$ *p*	$C_6H_4{\cdot}Cl$ *p*
f	$C_6H_4{\cdot}CH_3O$ *p*	C_6H_5
g	$C_6H_4{\cdot}CH_3O$ *p*	$C_6H_4{\cdot}CH_3O$ *p*
h	$C_6H_4{\cdot}CH_3O$ *p*	$C_6H_5{\cdot}CH_2$
i	$C_6H_4{\cdot}N(CH_3)_2$ *p*	C_6H_5
j	$C_6H_4{\cdot}N(CH_3)_2$ *p*	$C_6H_4{\cdot}Cl$ *p*
k	$C_6H_4{\cdot}Cl$ *p*	C_6H_5
l	$C_6H_4{\cdot}Cl$ *p*	$C_6H_4{\cdot}CH_3O$ *p*
m	$C_5H_4{\cdot}Cl$ *p*	$C_6H_5{\cdot}CH_2$
n	$C_6H_4{\cdot}CH_3$ *p*	$C_6H_4{\cdot}CH_3O$ *p*

IR measurements of arylidene-oxazolinones (**I**) showed ν C = O (α-lactone) at 1810 cm^{-1} (shoulder), together with absorption bands of C=O and C=N at 1750 cm^{-1} and 1640 cm^{-1} [4], respectively.

Hydrolysis of α-oxazolinones (**I**) (some representatives) by sodium methoxide was carried out to give the unsaturated amidoesters (**II**). It is noteworthy to mention that, only one methoxide molecule was consumed in this reaction and not two molecules as has been previously reported[5] in a similar case.

The structures of esters II was established by analysis and by studying their I.R. spectra which showed ν C=O as two bands at 1750 and 1670 cm^{-1} due to α-ester and -CONH absorptions respectively. Also I.R. spectra showed the stretching frequencies of N-H (sec. amides) and C-H (saturated) at 3200 cm^{-1} and 2950-2900 cm^{-1} regions.

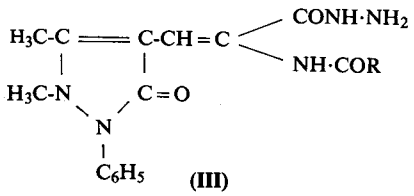


(**II**)

II	R
a	C_6H_4Cl *p*
b	$C_6H_4CH_3O$ *p*
c	C_6H_5
d	$C_6H_5{\cdot}CH_2$

The reaction of 4-arylidene oxaxolinones (**I**) with hydrazine hydrate was reported to yield aryl-idenehyppruric acid hydrazides[6].

In the present investigation, it was found that interaction of the oxazolinones (**I**) (some representative) with hydrazine hydrate, in ethanol, gave the corresponding hydrazides (**III**).



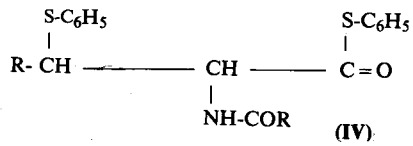
(III)

III	R
a	C_6H_5
b	C_6H_4·Cl *p*
c	C_6H_4·CH_3O *p*

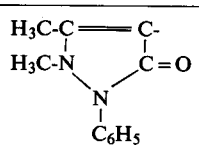
Structure of hydrazides **III** was based on i) Analytical data, ii) I.R. measurements which show the amide I band associated with the CONH group of acyclic secondary amides in the region 1690 cm^{-1}, besides two other bands which can be ascribed to NH stretching vibrations of the amino and imino groups, at 3100-3300 cm^{-1} region. iii) Hydrazides **IIIa-c** were also obtained by interaction of the esters **IIa-c** with hydrazine hydrate, the identity of the products was established by mixture melting points determinations.

It has been previously reported that same oxazolinones were reacted with thiophenol to give α -addition products. Therefore, the present investigation was extended to show the reaction of the oxazolinones (**I**) with thiophenol .

Thus, when oxazolinones (**I**) were left to react



(IV)

IV	R	R′
a		C_6H_5
b	〃 〃	C_6H_4·CH_3O *p*
c	〃 〃	C_6H_4Cl· *p*
d	C_6H_4·CH_3 *p*	C_6H_4·CH_3O *p*
e	C_6H_4·Cl *p*	C_6H_5·CH_2
f	C_6H_4·CH_3O *p*	C_6H_5·CH_2

with thiophenol, in dry benzene and in presence of piperidene, the corresponding 1-aryl-1,3-dithiophenyl-2-amidopropan-3-ones (**IV**) were obtained in good yield. In this reaction two molecules of the thiol were consumed, one of them reacted by addition and the other reacted as a nucleophilic reagent.

Elemental analysis of products IV gave correct values and I.R. measurements showed absorption bands at 1600 cm^{-1}, and 3150 cm^{-1} characteristic for O=C-NH and NH respectively. The newly prepared oxazolin derivatives were tested for antibacterial activities.

ANTIBACTERIAL ACTIVITY

The oxaxolin derivatives were tested for their antibacterial activities using 6 different bacteria. These bacteria were suspended in an agar culture media containing: 10 g/L glucose, 6 g/L peptone, 3 g/L yeast extract and 20 g/L agar (pH = 7). The organism-agar suspension were distributed in petridishes (15 diameter) and allowed to solidify before the addition of the solution of the compounds in the glass ring. The concentration of each compound was 0.01 g/100 m*l*. Then the dishes were incubated at 37° for 24 hr then the inhibition zones were estimated (Table I).

For these results we can conclude that:

1. *Escherichia coli* (E.C.), *Candida* (C.A.) and *Aspergillus niger* (A.N.) were not sensitive to these type of compounds.
2. The association of bridge double bond between: oxazolin-5-ones and the aromatic ring (**I**), CH attached to antipyrine ring and ester (**II**) and CH attached to antipyrine-ring and hydrazine (**III**), and sulphur compounds (**IV**) are associated with high activity against *Aerobacter aerognus* (A.A.) and this strains very stable for study of structure activity relationship of these types of compounds.
3. No correlation could be treated between activity and structure of the tested compounds when *Bacillus subtillis* (B.S.) and *Candida utilities* (C.U.) were used as screening system.

EXPERIMENTAL

All m.ps. are uncorrested. I.R. spectra were recorded by Zeiss Jena Spectrophotometer, Model U.R. 10. The NMR spectra were carried out in DMSO on a Varian EM 360-60 MHz.

Preparation of 2-oxazolin-5-ones (Ia-n)
General method

Table I. The antibacterial activities of oxazolin-5-one derivatives

Compound	Inhibition Zone in mm					
	B.S.	E.C.	A.N.	C.A.	A.A.	C.U.
Ia	+ +	+ +	+ +	+ +	+	+
b	+	+	+ + +	+	+	+
c	+	+	+	+	+	+
d	+	+	+	+	+ +	+
e	+ +	+ +	+	+ +	+ + +	+
f	+	+ + +	+ +	+ +	+ + +	+ + +
g	+	+	+	+	+ + +	+ + +
h	+	+ + +	+ + +	+	+ + +	+ +
i	+ + +	+ +	+ +	+	+ + +	+
j	+ + +	+ +	+	+	+ + +	+ + +
k	+ +	+ + +	+	+	+ + +	+
l	+ + +	+ + +	+	+	+ + +	+ +
m	+ +	+ + +	+	+ +	+ + +	+ + +
n	+ +	+ + +	+	+ +	+ + +	+ + +
IIa	+ + +	+ +	+	+ +	+ + +	+ +
b	+ + +	+ + +	+ + +	+	+ + +	+ + +
c	+	+ +	+ + +	+ + +	+ + +	+ +
d	+	+ +	+ +	+ + +	+ + +	+ + +
IIIa	+	+ +	+	+	+ +	+ + +
b	+	+ + +	+	+	+ + +	+ +
c	+ +	+ +	+ + +	+	+ + +	+ + +
IVa	+	+ +	+ +	+	+ + +	+ + +
b	+ +	+ +	+ +	+	+	+ +
c	+ + +	+ +	+ + +	+	+ + +	+ +
d	+ +	+ +	+ +	+ + +	+ + +	+ +
e	+ + +	+ +	+ + +	+	+ + +	+ + +
f	+	+ +	+ +	+ +	+ + +	+

B.S., *Bacillus subtilis;* C.A., *Candida,* E.C., *Escherichia coli;* A.A., *Aerobacter aerognus;* A.N., *Aspergillus niger;* C.U., *Candida utilities.*

A mixture of arylglycine (0.01 mole), and the aromatic aldehyde (0.01 mole) in acetic anhydride (20 m*l*) containing freshly fused sodium acetate (0.5 gm) was heated on a water bath at 90 °C for 2 hours. The reaction mixture was cooled, then the precipitated solid was cooled and recrystallized from proper solvent to give 2-oxazolin-5-one (**Ia-n**) (Tables II, VI).

Reaction of 2-aryl-4-arylidene-2-oxazoline-5-one with sodium methoxide

A mixture of oxazoline (**I**) (0.01 mole) and sodium methoxide (0.03 mole) in methanol (20 m*l*) was heated under reflux for 1 hour. The reaction mixture cooled and solidified with 5N hydrochloric acid. The precipitate was collected to give the α -arylamino-β -aryl-acrylic acid methyl ester (**II**) Tables III, VI).

Reaction of 2-aryl-4-arylidene-2-oxazoline-5-ones (I) with hydrazine hydrate

A mixture of 2-oxazoline-5-ones (**I**) (0.01 mole) and hydrazine hydrate (0.01 mole) in ethanol (20 m*l*) was heated under reflux on a water bath for 2 hours. The solid separated was collected and crystallized from ethanol to give the proper α -arylamino-β -arylacrylic acid (**III**) (Table IV, VI).

The same product can be prepared by interaction of the corresponding α -arylamido-β -aryl-

Table II. Mp, yield and elemental analysis data of 1-aryl-4-arylidene-2-oxazoline-5-ones (I)

Comp.	M.P.	Yield (%)	Formula	Analysis calc./found		
				C%	H%	N%
Ia	216	40	$C_{21}H_{16}N_3OCl$	64.04	4.07	10.67
				64.28	4.15	10.36
b	212	42	$C_{21}H_{17}N_3O_3$	70.19	4.73	11.70
				70.51	4.80	11.79
c	204	35	$C_{22}H_{19}N_3O_3$	70.78	5.09	11.26
				70.42	4.8	11.68
d	234	45	$C_{22}H_{19}N_3O_4$	67.87	4.88	10.80
				67.60	4.79	10.80
e	184	82	$C_{17}H_{12}NO_3Cl$	65.07	3.83	4.47
				65.31	3.99	4.62
f	204	80	$C_{17}H_{13}NO_3$	73.12	4.66	5.02
				73.01	4.89	5.50
g	180	85	$C_{18}H_{15}NO_4$	69.91	4.85	4.53
				69.51	4.35	4.66
h	162	70	$C_{18}H_{15}NO_3$	73.72	5.12	4.77
				74.06	5.12	4.77
i	214	75	$C_{18}H_{16}N_2O_2$	73.97	5.48	9.50
				73.62	5.13	9.21
j	212	78	$C_{18}H_{15}N_2O_2Cl$	66.16	4.60	8.57
				66.35	4.30	8.57
k	198	70	$C_{16}H_{10}NO_2Cl$	67.72	3.53	4.94
				67.99	3.18	4.52
l	178	83	$C_{17}H_{12}NO_3Cl$	65.07	3.83	4.47
				65.61	3.95	4.68
m	146	65	$C_{17}H_{12}NO_2Cl$	68.57	4.03	4.71
				78.50	4.38	4.61
n	194	75	$C_{18}H_{15}NO_3$	73.72	5.12	4.78
				73.98	5.51	4.39

Table III. Mp, yield and elemental analysis data of α-arylamino-β-arylacrylic acid methyl esters (II)

Comp.	M.P.	Yield (%)	Formula	Analysis calc./found		
				C%	H%	N%
IIa	198	70	$C_{22}H_{20}N_3O_4Cl$	62.05	4.70	9.87
				62.41	4.83	10.13
b	183	65	$C_{23}H_{23}N_3O_5$	65.56	5.46	9.98
				65.19	5.29	9.81
c	182	62	$C_{22}H_{21}N_3O_4$	67.52	5.37	10.74
				67.81	5.19	10.59
d	220	62	$C_{23}H_{23}N_3O_4$	68.15	5.68	10.37
				68.38	5.19	10.82

Table IV. Mp. yield and elemental analysis data of α -arylamino- β-arylacrylic acid (III)

Comp.	M.P.	Yield (%)	Formula	Analysis calc. / found		
				C%	H%	N%
IIIa	224	70	$C_{21}H_{21}N_5O_3$	64.45	5.37	17.50
				64.25	5.19	17.78
b	222	75	$C_{21}H_{20}N_5O_3Cl$	59.22	4.70	16.45
				59.54	4.51	16.68
c	230	70	$C_{22}H_{23}N_5O_4$	62.71	5.46	16.63
				62.38	5.72	16.51

Table V. Mp, yield and elemental analysis data of 1-aryl-1,3-dithiophenyl-2-amidopropan-3-ones (IV)

Comp.	M.P. C°	Yield (%)	Formula	Analysis calc. / found			
				C%	H%	N%	S%
IVa	96	63	$C_{33}H_{29}N_3O_3S_2$	68.39	5.01	7.25	11.06
				68.51	5.12	7.11	11.17
b	192	60	$C_{34}H_{31}N_3O_4S_2$	67.00	5.09	6.90	10.51
				67.17	5.12	6.73	10.29
c	180	65	$C_{33}H_{28}N_3S_2ClO_3$	64.55	4.56	5.85	10.43
				64.38	4.62	5.98	10.53
d	154	62	$C_{30}H_{27}NO_3S_2$	70.18	5.26	2.73	12.48
				70.31	5.41	2.59	12.61
e	82	60	$C_{29}H_{24}NO_2S_2$	72.20	4.98	2.90	13.28
				72.34	5.07	2.81	13.13
f	142	62	$C_{30}H_{27}NO_3S_2$	70.18	5.26	2.73	12.47
				70.52	5.37	3.12	12.03

Table VI. The ^{1}H-NMR data of the synthesized oxazolin-5-one derivatives

Compound	^{1}H-NMR in ppm
Ia	2.25(s,2CH_3,6H), 5.3(s,CH,1H), 7.39(s,C_6H_5,5H) 7.82(m,C_6H_4,4H).
b	2.25(s,2CH_3,6H), 5.3(s,CH,1H), 7.39(s,2C_6H_5,10H).
c	2.23(s,2CH_3,6H), 4.2(s,CH_2,2H), 5.3(s,CH,1H), 7.38(s,2C_6H_5,10H).
d	2.24(s,2CH_3,6H), 3.4(s,OCH_3,3H), 5.2(s,CH,1H), 7.38(s,C_6H_4,4H).
e	3.2(s,OCH_3,3H), 5.2(s,CH,1H), 7.25(s,2C_6H_4,8H).
f	3.4(s,OCH_3,3H), 5.2(s,CH,1H), 7.24(s,C_6H_4,4H), 7.43(C_6H_5,5H).
g	3.32(s,2OCH_3, 6H), 5.2(s,CH,1H), 7.32(s,2C_6H_4,8H).
h	3.39(s,OCH_3,3H), 4.3(s,CH_2,2H), 5.2(s,CH,1H), 7.32(s,C_6H_4,4H), 7.88(s,C_6H_5,5H).
i	3.24(s,2CH_3,6H), 5.3(s,CH,1H), 7.26 (C_6H_4,4H), 7.29(s,C_6H_5,5H)
j	3.27(s,2CH_3,6H), 5.2(s,CH,1H), 7.38 (s,2C_6H_4,4H).
k	5.37(s,CH,1H), 7.32(s,C_6H_4), 7.31(s,C_6H_5,5H).
l	3.28(s,OCH_3,3H), 5.31(s,CH,1H), 7.32(s,2C_6H_4, 8H).
m	4.1(s,CH_2,2H), 5.2(s,CH,1H), 7.18(s,C_6H_4,4H), 7.41(s,C_6H_5,5H).
n	3.27(s,2CH_3,6H), 5.37(s,CH,1H), 7.32(s,2C_6H_4,8H).
IIa	2.21(s,2CH_3,6H), 3.74(s,CH_3,3H), 5.2(s,CH,1H), 7.64(s,2C_6H_5,10H), 10.78(s,NH,1H).
b	2.27(s,2CH_3,6H), 3.71(s,CH_3,3H), 5.33(s,CH,1H), 7.71(s,C_6H_5,5H), 7.4(s,C_6H_4,4H), 10.72(s,NH,1H).

c	2.25(s,2CH_3,6H), 3.68(2,2CH_3,6H), 5.36(s,CH,1H), 7.73(s,C_6H_5,5H), 7.32(s,C_6H_4,4H), 10.75 (s,NH,1H).
d	2.23(s,2CH_3,6H), 3.52(s,CH_3,3H), 4.2(s,CH_2,2H), 5.24(s,CH,1H), 7.73(s,2C_6H_5,10H), 10.73 (s,NH,1H).
IIIa	2.23(s,2CH_3,6H), 5.32(s,CH,1H), 7.72(s,2C_6H_5,10H), 7.53(s,NH_2,2H), 8.73(s,NH,1H), 10.23(b.s,NH, 1H).
b	2.24(s,2CH_3,6H), 5.33(s,CH,1H), 7.73(s,C_6H_5,5H), 7.58(s,C_6H_4,4H) 7.52(s,NH_2,2H), 8.72(s,NH,1H), 10.34(b.s,NH,1H).
c	2.21(s,2CH_3,6H), 3.75(s,CH_3,3H), 5.31(s,CH,1H), 7.71(s,C_6H_5,5H), 7.57(s,C_6H_4,4H), 7.5(s,NH_2,2H), 8.75(s,NH,1H), 10.27(b.s,NH,1H).
IVa	2.23(s,2CH_3,6H), 4.3(s,2CH,2H), 7.73(s,4C_6H_5,20H), 10.73(b.s,NH,1H).
b	2.23(s,2CH_3,6H), 3.78(s,CH_3), 4.23(s,2CH,2H), 7.72(s,3C_6H_5,15H), 7.32(s,C_6H_4,4H), 10.71(b.s,NH, 1H).
c	2.25(s,2CH_3,6H), 4.25(s,2CH,2H), 7.72(s,3C_6H_5,15H), 7.73(s,C_6H_4,4H), 10.85(bs,NH,1H).
d	2.23(s,CH_3,3H), 3.72(s,CH_3,3H), 4.27(s,2CH,2H), 7.72(s,2C_6H_5,10H), 7.58(s,2C_6H_4,8H), 10.82(b.s, NH,1H).
e	4.25(s,2CH,2H), 4.52(s,CH_2,2H), 7.78(s,3C_6H_5,15H), 7.42(s,C_6H_4,4H), 10.82(b.s,NH,1H).
f	3.72(s,CH_3,3H), 4.23(s,2CH,2H), 4.53(s,CH_2,2H), 7.72(s,3C_6H_5,15H), 7.53(s,C_6H_4,4H), 10.85(b.s,NH, 1H).

acrylic acid methyl ester (**II a-c**) (0.01 mol) with hydrazine hydrate (0.01 mole) in methyl alcohol (30 m*l*). The reaction mixture was heated for 3 hrs. under reflux, cooled and the solid separated was collected, then crystallized from ethanol to give the same product (**III**) (m.p. and mixture m.p.).

Reaction of 2-aryl-4-arylidene-2-oxazoline-5-one (I) with thiophenol

A mixture of (I) (0.01 mole), thiophenol (0.02 mole) and few drops of piperidene in dry benzene. After 1/2 hour, a semi-solid mass of crystals was obtained which collected and crystallized from hot benzene to give (**IV a-f**) as colourless crystals (Tables V, VI).

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