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Synthesis and Characterization of Novel Compounds Containing of Imidazolidinone and Oxazepine Rings

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Abstract

The compound 3-[4-(4"-methoxy benzoyloxy) benzylideneamino]-2-thioxo-imidazolidine-4-one [III] was prepared from the cyclization of thiosemicarbazone [II] with ethyl α -chloroacetate in the presence of fused sodium acetate. Treatment the later compound with acetic anhydride yielded the corresponding 1-Acetyl-3-[4- (4"- methoxy benzoyloxy) benzylideneamino] – 2 – thioxo -imidazolidine-4-one [IV]. 1,3-Oxazepine derivatives $[V]_{a-d}$ and $[VI]_{a-d}$ are obtained from the reaction of compounds[III] and [IV] with different acid anhydrides, in dry benzene. The FTIR and ^{1}HNMR spectroscopy are indicated a good evidence for the formation of the synthesized compounds. Some of the synthesized compounds have been screened against *E.coli* , *Staph. aureus* , *Psenudomonsaeruginosa and Bascillus cereus* . They exhibited moderate to weak antibacterial activity unless compound $[V]_d$ did not show any biological activity.

Key words: imidazolidenone, oxazepine

Introduction

2-Thioxo-imidazolidin-4-one are imidazolidine ring that contain two groups thion(C=S) and carbonyl (C=O) at position, 2 and 4, respectively. It is well known that 2-thioxo-4-imidazolidinone derivatives display a wide range of biological properties.[1,2]

Various methods are used for the preparation of 2-thioxo-imidazolidin-4-one among these; Treatment of arylisothiocyanate with amino acid under different conditions [3, 4]. Also, 2-thioxo-imidazolidin-4-One can be prepared by reaction of thiosemicarbazone with ethylα -chloroacetate in the presence of CH_3CO_2Na under reflux [1].

1, 3-Oxazepine is non-homologuos seven member rings, that contains oxygen at position 1 andnitrogen at position 3. Oxazepine is used in the medical field and has been much chemical and biological studied. Many workers synthesized and studies the oxozepine derivatives mentioned as in the literates [5-8].

The aim of this work is to synthesis and characterization a novel compound containing imidazoliden-4-One and 1, 3-Oxazepine units in the same molecule.

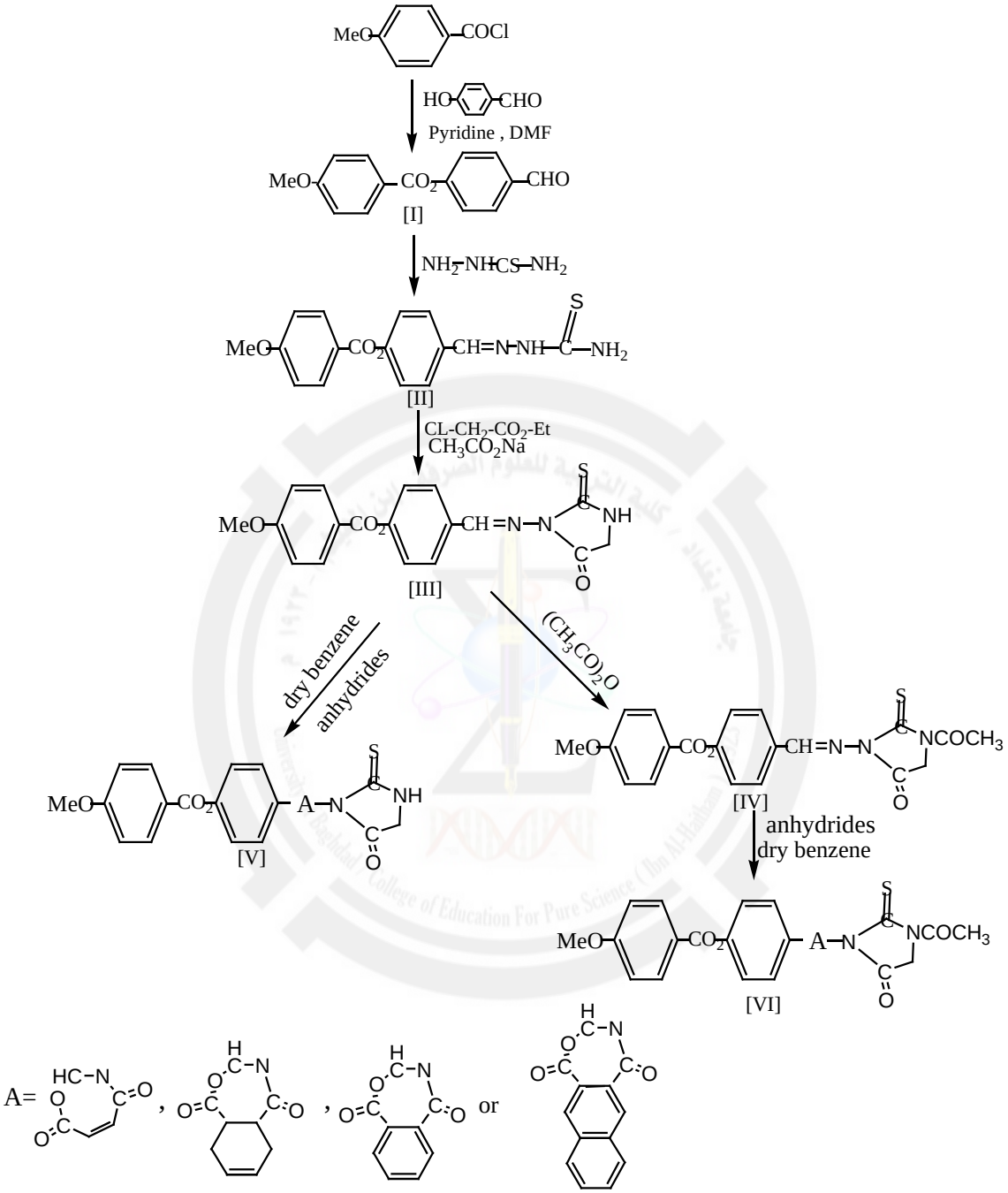
Experimental

Materials: All the chemicals were supplied from Fluke, GCC and Aldrich Chemicals Co. and used as received.

Techniques: FTIR spectra were recorded using potassium bromide discs on a Shimadzo (Ir prestige-21) . ^{1}HNMR spectra were carried out by company: Bruker , model: ultra-shield 300 MHz , origin : Switzerland and are reported in ppm(δ), DMSO was used as a solvent with TMS as an internal standard . Measurements were made at chemistry department, Al-albyat University; uncorrected melting points were determined by using Hot-Stage, Gallen Kamp melting point apparatus.

General procedures

The new compounds [II]-[VI] were synthesized according to scheme 1.



Scheme 1

Synthesis of 4-(4`-methoxy benzoyloxy) benzaldehyde [I]

Anisoyl chloride (0.01mol) was added to a stirred solution of 4-hydroxy benzaldehyde (0.01mol) and dry pyridine (1mL) in dry dimethyl formamide (DMF) (10 mL) at (5-10°C). Stirring was continued for 3hrs at the same temperature. The resulting mixture was poured into 100 mL of 10% HCl . The precipitate was filtered and washed with solution of 10% $NaHCO_3$ and water for several times [9] ,dried and recrystallized from ethanol . m.p 90 ^{0}C , yield 95%.

Synthesis of 4-(4-methoxy benzoyloxy)benzaldehyde thiosemicarbazone [II]

A mixture of aromatic aldehyde [I] (0.001 Mole) , thiosemicarbazide (0.001 Mole) in ethanol (3mL) was heated under reflux for 4hr, then cooled .The yellow solid formed was filtered ,dried and purified by recrystallization from ethanol to give compound [II]. m.p 200 ^{0}C , yield72%.

Synthesis of 3-[4-(4=-methoxy benzoyloxy) benzylideneamino]-2-thioxo-imidazolidine-4-one [III]

A mixture of compound [II] (0.001mole), ethyl chloro acetate (0.001mole) and fused acetate (0.003mole) in ethanol was heated under reflux for 4hrs , then cooled and poured into water. The resulting pale yellow solid was filtered off, washed with water, dried and recrystallized by ethanol to give compound [III] . m.p 238 ^{0}C , yield 77%.

Synthesis of 1-Acetyl-3-[4- (4=- methoxy benzoyloxy) benzylideneamino] – 2 – thioxo - imidazolidine-4-one [IV]

A solution of [III] (0.01mole) in acetic anhydride (25mL)was heated under reflux for 4hrs, then cooled and poured onto ice-water .The resulting orange product was filtered off ,washed with water, dried and recrystallized by ethanol to give compound [IV] . m.p 225^{0}C , yield 58% .

Synthesis of 1,3-oxazepine derivatives [V]$_{a-d}$ and [VI]$_{a-d}$

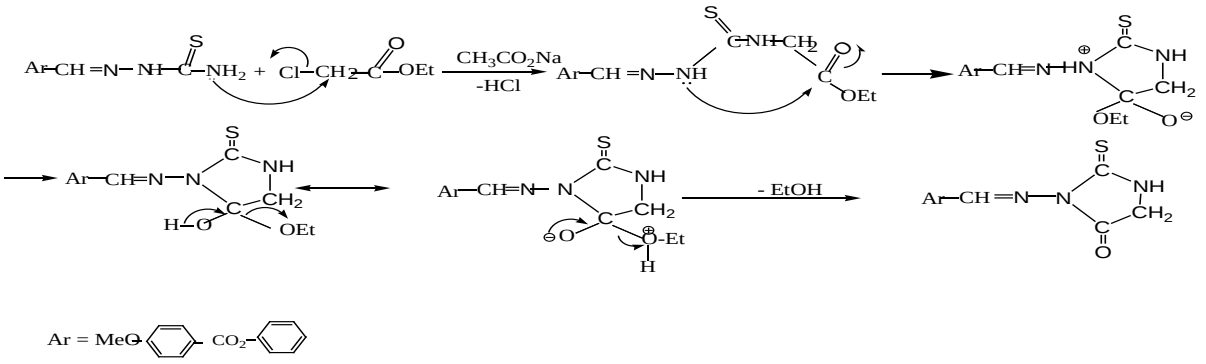
A mixture of (0.001mol) of Schiff bases [III] or [IV] and (0.001mole) of appropriate acid anhydrides in dry benzene (5mL) was refluxed for 6 hrs , the solvent was removed and the resulting colored crystalline solid recrystallized from ethanol. The physical data of all synthesized 1,3-oxazepines are listed in Table (1) .

Result and discussion

Thiosemicarbazone [II] were synthesized by refluxing equimolars of aromatic aldehyde [I] and thiosemicarbazide in ethanol .

This compound was identified by its melting point and FTIR spectroscopy. FTIR absorption-spectrum showed the disappearance of aldehydic (C=O) absorption band at 1695 cm^{-1} together with appearance of new absorption stretching band at1699 cm^{-1} which is assigned to C=N stretching[10]. The spectrum showed many peaks in the region 3445-3105cm^{-1} which could be attributed to asymmetric and symmetric stretching vibration of NH and NH_2 groups and two sharp peaks at 1722cm^{-1} and 1186cm^{-1} due to ester and thion groups , respectively.

Compound [III] was synthesized from the reaction of thiosemicarbazone [II] with ethyl chloroacetate in fused sodium acetate; the suggested mechanism of this reaction may be shown as follows Scheme 2.



Schem 2

The structure of the imidazolidenone [III] was identified by its melting point , FTIR and ¹HNMR spectroscopy. The FTIR spectrum of this compound showed the disappearance of absorption bands of the NH_2 group ,in the thiosemecarbazone and appearance a sharp new absorption stretching bands at 1634 cm^{-1} due to C=O group of imidazolidenone ring. Also showed a weak stretching band at 3069 cm^{-1} and a sharp peak at1200 cm^{-1} could be attributed to NH and C=S groups, respectively.

The ^{1}HNMR spectrum of compound $[III]_a$ shows the following signals : eight aromatic protons appeared as pair of doublet at δ 7.12-8.28 ppm ,two sharp singlet at δ 8.44 ppm and δ 11.9 ppm that could be attributed to the one proton of CH=N and one proton of NH, respectively. The spectrum shows also two sharp singlet at δ 3.88 ppm an δ 3.23 ppm due to the three protons of OCH_3 and two protons of CH_2 groups, respectively.

Treatment the later compound with acetic anhydride yielded the corresponding 1-Acetyl-3-[4- (4"- methoxy benzoyloxy) benzylideneamino] – 2 – thioxo -imidazolidine-4-one [IV]. The FTIR spectrum indicated the disappearance the characteristic stretching band of the NH group with appearance a good band at 1720 cm^{-1} due to N-acetyl (N-C=O) stretching vibration.

The ^{1}HNMR of this compound show the following features: two pairs of doublet of doublets in the region δ6.79-8.09 ppm which can be attributed to eight protons of two p-substituted benzene rings having different substituents at positions I,4 . A sharp singlet at δ 8.79 ppm that could be attributed to the one proton of CH=N. The spectrum shows a quartet signal and a triplet signal at δ 4,31-4.49 ppm and δ 2.05-2.22 ppm due to two protons of CH_2 and three protons of $NCOCH_3$ groups, respectively . Besides a sharp singlet at δ 3.87 ppm for the three protons of OCH_3.

The 1,3-oxazepine derivatives were obtained by addition reaction of Schiff bases with different anhydrides in dry benzene, The new 1,3-oxazepine derivatives [V] and [VI] were synthesized by refluxing compound [III] or [VI] with different anhydride (maleic, 2,3,5,6-tetrahydrophthalic , phthalic or naphthalic anhydride) in presence of dry benzene. The characteristic FTIR absorption bands of these compounds were confirmed from the disappearance of band due to C=N of Schiff bases and other peaks characterized of cyclic anhydride of the starting materials together with appearance two bands characteristic of two carbonyl groups of oxazepine ring. The spectral data of FTIR for new oxazepine compounds are listed in Table(2).

The ^{1}HNMR spectrum of compound $[VI]_d$ (in DMSO) shows a singlet signal of N-CH proton absorbed at δ 7.22 ppm, the aromatic ring protons appear as multiplet in the region (δ 6.79-8.56) ppm , a singlet signals at δ3.87 ppm and 3.83 for OCH_3 protons absorbed . The spectrum shows a quartet signal and a triplet signal at δ 4.31-4.49 ppm and δ 2.05-2.22 ppm due to two protons of CH_2 and three protons of $NCOCH_3$ groups, respectively

Biological Activity

The antibacterial activity of the synthesized compounds was performed according to the agar diffusion method [11]. The prepared compounds were tested against *E.coli* , *Staph. aureus* , *Psenudomonsaeruginosa and Bascillus cereus.* Each compounds was dissolved in DMSO to give concentration 1ppm. The plates were then incubated at 37 ^{0}C and examined after 24 hrs. The zones of inhibition formed were measured in millimeter and are represented by (-), (+) and (+ +) depending upon the diameter and clarity as in Table (3).

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Table (1): Physical data of oxazepine compounds.

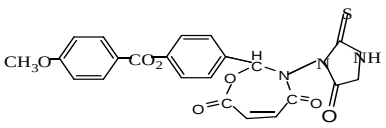
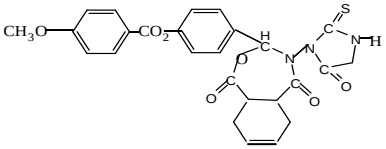
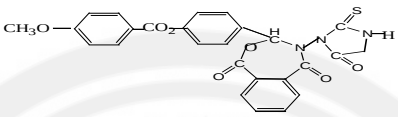
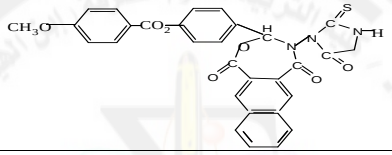
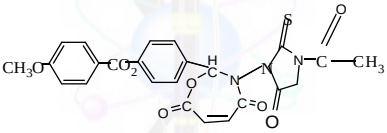
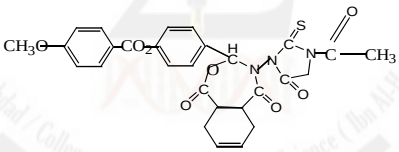
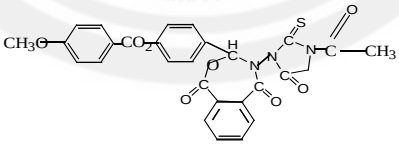
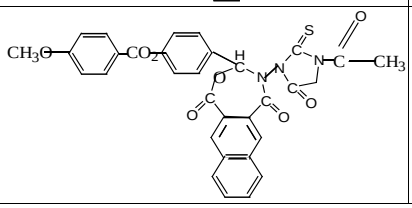
Comp. No.	Nomenclature	Structural formula	Molecular formula	M. P ^{0}C	Yield %	Color
$[V]_a$	2-[4-(4=-methoxy benzoyloxy) phenyl]-3-(2-thioxo-imidazolidine-4-one-3-yl)-2,3-dihydro-1,3-oxazepine-4,7-diones		$C_{22}H_{17}N_3O_7S$	228-230	54	Off white
$[V]_b$	2-[4-(4=-methoxy benzoyloxy) phenyl]-3-(2-thioxo-imidazolidine-4-one-3-yl)-2,3-dihydro-5,6-cyclohexane[1,2e]-1,3-oxazepine-4,7-diones		$C_{26}H_{23}N_3O_7S$	252-256	70	Off white
$[V]_C$	2-[4-(4=-methoxy benzoyloxy) phenyl]-3-(2-thioxo-imidazolidine-4-one-3-yl)-2,3-dihydro-benz[1,2e]1,3--oxazepine-4,7-diones		$C_{26}H_{19}N_3O_7S$	206-208	61	yellow
$[V]_d$	2-[4-(4=-methoxy benzoyloxy) phenyl]-3-(2-thioxo-imidazolidine-4-one-3-yl)-2,3-dihydro-naphth[2,3e]-1,3-oxazepine-4,7-diones		$C_{30}H_{21}N_3O_7S$	195-198	82	yellow Pale
[VI]a	2-[4-(4=-methoxy benzoyloxy) phenyl]-3-[1-acetyl (2-thioxo-imidazolidine-4-one-3-yl)-2,3-dihydro-1,3-oxazepine-4,7-diones		$C_{24}H_{19}N_3O_8S$	178-180	57	yellow
$[VI]_b$	2-[4-(4=-methoxy benzoyloxy) phenyl]-3-[1-acetyl (2-thioxo-imidazolidine-4-one-3-yl)-2,3-dihydro-5,6-cyclohexane[1,2e]-1,3-oxazepine-4,7-diones		$C_{28}H_{25}N_3O_8S$	172-176	59	Yellow dark
$[VI]_C$	2-[4-(4=-methoxy benzoyloxy) phenyl]-3-[1-acetyl (2-thioxo-imidazolidine-4-one-3-yl)-2,3-dihydro-benz[1,2e]-1,3-oxazepine-4,7-diones		$C_{28}H_{21}N_3O_8S$	205-209	68	Glow yellow
$[VI]_d$	2-[4-(4=-methoxy benzoyloxy) phenyl]-3-[1-acetyl (2-thioxo-imidazolidine-4-one-3-yl)-2,3-dihydro-naphth[2,3e]-1,3--oxazepine-4,7-diones		$C_{32}H_{23}N_3O_8S$	234	63	yellow

Table (2) : FTIR spectral data of oxazepine compounds.

Comp. No.	νNH	νC-H Aliph.	νC=O lactone,lactome of oxazepine	νC=O amid exocyclic	νC=O imidazolidinone	νC=C arom.
$[V]_a$	3069	2976,2843	1770 , 1710	-	1634	1598
$[V]_b$	3098	2966,2862	1765 , 1695	-	1634	1597
$[V]_c$	3078	2960,2843	1765 , 1695	-	1633	1599
$[V]_d$	3067	2989,2842	1771 , 1726	-	1634	1599
$[VI]_a$	-	2958,2840	1732 , 1697	1705	1637	1604
$[VI]_b$	-	2942,2825	1728 , 1695	1719	1655	1605
$[VI]_c$	-	2940,2854	1768 , 1690	1721	1654	1604
$[VI]_d$	-	2926,2852	1770 , 1684	1701	1640	1605

Table (3) : Biological activities of some of synthesized compounds.

Comp. No.	*Staphylococcus aureus(G+)*	*Bascillus cereus (G+)*	*Escherichichia coli(G-)*	*Psenudomonsaeruginosa(G-)*
[II]	+ +	+ +	+ +	–
[III]	–	+ +	+	–
[IV]	+	+	+	+
$[V]_d$	–	–	–	–
$[V]_a$	+ +	+	+	–
$[VI]_c$	–	++	–	–

Key to symbols : Moderately active = + +(11-15) mm and slightly active = + (5-10)

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تحضير وتشخيص مركبات جديدة تحتوي على حلقتي الايميدازولدينون والاكسازبيين

طالب رشيد محسن ، جمبد هرمز توما ، عبد الجبار عبد القادر مخلص
قسم الكيمياء ، كلية التربية ابن الهيثم ،جامعة بغداد

الخلاصة

حضرالايميدازولدين-4-ون [III] من الغلق الحلقي للثايوسيميكاربازون[II] مع اثيل كلورو اسيتات بوجود خلات الصوديوم المنصهرة تمت معاملة المركب الاخير مع انهيدريد الخليك لينتج المركب المقابل[VI]. حضرت مشتقات الاوكسازبين[V] و [VI] من تفاعل المركب [III] و [IV] مع انهيدريدات متنوعة على التوالي في البنزين الجاف. أثبتت صحة التراكيب للمركبات المحضرة باستعمال طيفFTIR وطيف الرنين النووي المغناطيسي ^{1}NMR H . درست الفعالية البايولوجية لبعض من المركبات المحضرة ضد انواع من البكتريا *E.coli , Staph. Aureu, Bascillus cereus Psenudomonsaeruginosa* وبينت النتائج ان اغلب المركبات اظهرت فعالية بايولوجية ضد البكتريا المستخدمة تراوحت بين المتوسطة الى الضعيفة ولم يظهر المركب $_{d}$[V] اي فعالية ضد هذه الانواع من البكتريا

الكلمات المفتاحية : الايميدازولدين، الاوكسازبين