تحضير و تقييم الفعالية المضادة للبكتريا لبعض مشتقات ثنائية 4,1-بيوتان-4,3,1-اوكسادايزول

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الخلاصة

تم تحضير سلسلة من مشتقات ثنائية 4,1-بيوتان-4,3,1-اوكسادايزول [IIIa-j] من حمض الادبيك ثنائي الهيدازيد مع بعض الحوامض الاروماتية المختلفة بوجود كلوريد الفسفوريل، و قد تم تشخيص هذه السلسلة بأستخدام تقنية الاشعة تحت الحمراء و تحليل العناصر و طيف الكتلة.

و اظهرت الدراسة ان قسم -(Gram و + Gram)و قد تم دراسة تأثير هذه المركبات على الفعالية المضادة للبكتريا من نوع من هذه المركبات لها فعالية بايولوجية ضد انواع من البكتريا.

Synthesis and Antimicrobial Evaluation of Some Bis-1, 3, 4-Butane-1-3, 4-Oxadiazole Derivatives

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Abstract

A series of new Bis-1,4-Butane -1,3,4 – Oxadizole derivatives [III a-j] were synthesized from adipic acid dihydrazide and different aromatic acids in the presence of phosphours oxychloide. There compounds were characterized by their IR, microanalysis, and mass spectral data.

In vitro antimicrobial were synthesized. In vitro antimicrobial activity of these compounds against (Gram negative) and (Gram positive) were reported, some of these compounds prepared derivatives exhibited antimicrobial activity.

Introduction

Many compounds contain 1,3,4-oxadiazole ring system which possesses possible biological activity (1-2-3). 3-substituted aminomethyl-5-substitued-1,3-4-oxadiazole-2-thione are tuberculostatic (4) and fungicidal, similarly 3,5-disubstituted – 1,3,4- oxadiazole-2-thione have strong pesticidal (5) and hyp-oglycemic (6) activity.

Some are bis-(5-mercapto-1, 3, 4- oxadiazole-2-yl) alkanes and they revealed the antifungal activity (7); they also showed that a slight increase in activity takes place as the number of methylene groups increases (8).

In this work ethyl adipate [I] readily reacted with hydrazine hydrate to give adipic dihydrazide [II], phosphours oxychloride was employed in the preparation of the bis-1,4-butane -1,3,4-oxadizole derivatives [III a-j] from adipic dihydrazide and different aromatic acids (scheme 1).

All compounds were isolated and purified in satisfactory yield and their physical data element analysis, melting point mass-spectrum as shown in Table (1), and IR spectra are listed in the experimental section.

Antimicrobial activity of some synthesized compounds was carried out against three types bacteria: *Staphylococcus aurevs* ATCC 25923, Escherichia *coli* ATCC 29522, and *Pseudomonas aeruginosa* ATCC 27853.

Some of the synthesized compounds [IIIa-j], showed antibacterial activity as shown in Table (1).

Experiment

The purity of the resultant compounds was checked by the melting points which are uncorrected and were taken on a“Electrothermal“melting points apparatus (Mettle), micro analytical samples were analyzed by Iraqi Petroleum Company, mass spectra were recorded on shimadzo Qp 1000, Gas mass spectrometer (Gc-Ms), by using a direct insertion system from the range of m/z 10-1000 and ionization energy (EI), of 20ev or 70ev.

IR spectra were measured by using a perkin –Elmer 1310 infrared spectropho-meter on KBr disc.

Preparation of adipic dihydrazide [II] General Procedure (9)

A mixture of diethyl adipate [1] (0.01 mole) and excess hydrazine hydrate (0.02mole) were refluxed for 30 min. The separated preapilate were filtered and washed with absolute ethanol and used without further purification , yield 100% , m.p. = 182°c lit, 182°c (10).
IR $(KB_r)_{\nu\ max}$ of these hydrazide show stretching bands (3300,3160,3060cm^{-1}) NH_2 and N-H groups, (1603 cm^{-1}) C=0 amide I , (1540 cm^{-1}) C=0 amide II.

Bis-1,4-(5-5-aryl -1,3,4-oxadizole-2yl) butane [III a-j].

A mixture of acid dihydrazide [II] (0.01mole) aromatic acid (0.02mole) and phosphours oxychloride (5ml) was refluxed gently at (80-90) °C for 3 hours. After cooling, the mixture was poured into ice water and made basic by adding sodium bicarbonate solution. The resulting solid was filtered, dried and recry-stallized from a proper solvent to give the desired oxadiazole derivatives.

IR$(KB_r)_{\nu\ max}$ of these compounds show bands (2900-2825 cm^{-1}) C-H aromatic ;(1600-1570 cm^{-1}) C = N and C = C ; (1250-1200 cm^{-1}) C-O-O, another physical data are shown in Table (1).

Bacterial Strains and Culture Media

For antibacterial activity we used the following microorganism:
Staphylococcus aureus ATCC 25923, Escherichia *coli* ATCC 25922 and *Pseudomonas aeruginosa* ATTC 27853, these were cultivated in Typticase Soya agar (Difco), typticase soy broth (Difco).

Antimicrobial activity

The compounds of Table (1) were screened for their inhibitory effects against S.aureus, E. coli and Ps. aeruginosa by agar diffusion technique (11).

The chemical compounds were dissolved in DMSO to give a final concentration of 1mg/ml. A 20ml of the sterilize trypticase Soya agar media was poured in a glass plates of 9 cm in diameter and after solidification aloopful of overnight culture of each test org. was streaked on the surface of the predried agar plates, wells of 6mm were maele in the agar media by cork borer after the removal of the agar pillets, 100mg from each test compound were placed in each well in a duplicate.

The plates then were incubated at 37°C for 24 hours to show the inhibition zone.

Streptomycin sulfate in a concentration of (0.1 mg/ml) were used as a standard growth inhibitor for the bacteria.

The inhibitory effect of DMSO was also examined which shows no inhibitory effect against the test organisms.

Results and Discussion

Synthesis of the compounds

The synthesis of the bis-1,3 (5, 5aryl -1,3,4-oxadiazole-2-yl) butane derivatives [IIIa-j] were accomplished in accordance with the sequence of reactions depicted in Scheme 1

Ethyl diester [I] were refluxed with 98% hydrazine hydrate to give after 30 min. the expected hydrazide [II], which was identified by melting point 182°C.lit, 182°C and by infrared spectroscopy .

The 2,5- disubstituted – 1,3,4-oxadiazole were prepared by a route in which the acid dihydrazide [II] was condensed with the appropriate aromatic acid in the presence of phosphours oxychloride .

The structures of 1,3,4-oxadiazole derivatives [IIIa-j] were confirmed by infrared, C,H,N-analysis and mass spectroscopy .

The IR spectra of [IIIa-j] were devoided of the amide bands in the spectrum of acid dihydrazide [II] at (3300,3160,3050 cm^{-1}) and (1630 cm^{-1}) but showed (C═ N) stretching vibration band (12) ,in the range(1570-1600 cm^{-1}) a band in the range (1200-1250 cm^{-1}) of C-O-C stretching vibration combined with N-N band of 1,3,4-oxadiazole moiety (13,14). Evidence of the presence of aromatic ring which is the presence of C ═ C aromatic ring which is the presence of C ═ aromatic stretching band (1400-1570 $cm^{-1)}$ and out of plane bending substituted aromatic systems in the range (700-850 $cm^{-1)}$. Further structural proof for the oxadiazole derivatives was obtained from mass spectra, the fragmentation of 2,5disubstituted- 1,3,4- oxadiazole is specific and indicative for the structure (15). The most informative fragments that were observed in the mass spectra of 1,3,4- oxadiazole derivatives are listed in Table (1) which gives a strong evidence for the presence of oxadiazole ring.

Antimicrobial activity

Table (1) shows that oxadiazole derivatives containing aryl substituent 64 (a, c, d, f, g, h, I, j) showed antimicrobial activity towards all kinds of bacteria used, although their effect is less than that of the standard used, the resistance of some of these bacteria may be due to the permeability of these compounds through the cell wall (16).

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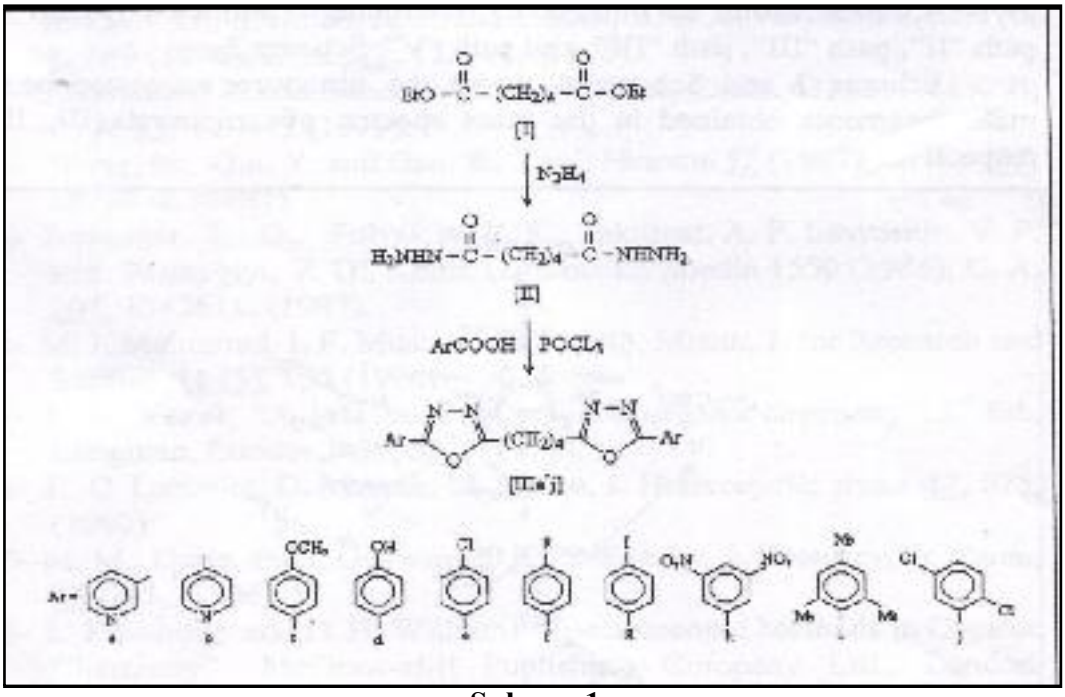

Scheme 1

Table (1): The diameter of growth inhibition zone

Comp.	S. aureus	E. coli	Ps. aeruginosa
III a	___*	11.0	10.0
III c	13.0	12.0	12.0
III d	13.0	10.0	10.0
III e	___	___	___
III f	13.0	___	12.0
III g	12.0	13.0	9.0
III h	12.0	___	___
III i	13.0	10.0	10.0
III j	11.0	8.0	___
Streptomycin Sulphate	21.0	23.0	21.0

*=Growth (no inhibition)