Synthesis and Antimicrobial Testing of Some 1,3,4-Oxadiazolines

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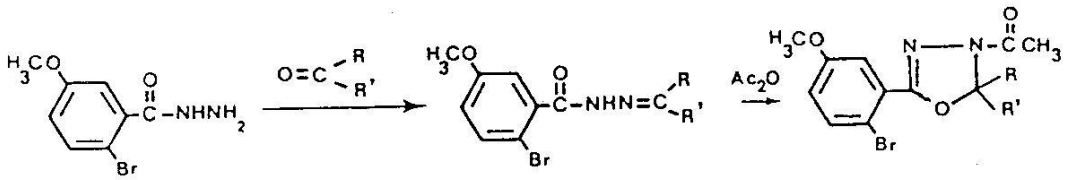
1,3,4,-Oxadiazole-2-thione derivatives have been reported to possess broad spectrum biological activities such as analgesic, muscle relaxant, tranquilizing properties [1-3], central nervous depressant activity [4], bactericidal [5,6] and fungicidal [5,7] properties. Moreover, several Mannich bases have been reported to exhibit antimicrobial activity [8,9]. These observations prompted the synthesis of unreported series of 1,3,4-oxadiazole derivatives as possible antimicrobial agents.

Treatment of 2-bromo-5-methoxybenzoylhydrazine with some selected carbonyl compounds in ethanol at reflux temperature afforded the corresponding hydrazones (Ia-e) table-I, in nearly quantitative yields. Treatment of the hydrazones (Ia-e) with excess acetic anhydride yielded the corresponding 5-(2-bromo-5-methoxyphenyl)-3-acetyl-2-substituted-1,3,4-oxadiazoline derivatives (IIa-e) table-II.



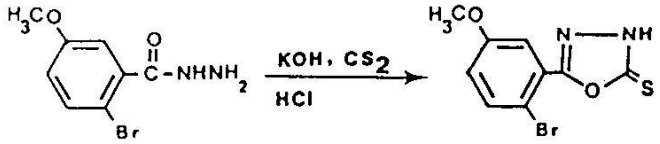
(Ia-e) (IIa-e)

The method of Young et al. [10] was adopted for the synthesis of 5-(2-bromo-5-methoxyphenyl)-1,3,4-oxadiazoline-2-thione (III) by condensation of 2-bromo-5-methoxybenzoylhydrazine with potassium hydroxide and carbon disulphide in ethanol followed by acidification.

The Mannich bases, 5-(2-bromo-5-methoxyphenyl)-3-substituted aminomethyl-1,3,4-oxadiazoline-2-thiones (IIIa-h) table-III and (IVa-d) table-IV, were prepared by treating an ethanolic solution of 5-(2-bromo-5-methoxyphenyl)-1,3,4-oxadiazoline-2-thione (III) and formaldehyde solution with the appropriate primary or secondary amine at ambient temperature.

Antimicrobial Testing

The agar diffusion method [11] was adopted for testing the preliminary antimicrobial activity of representative compounds against gram-positive bacteria (Staphylococcus aureus NCTC 7447), gram-negative bacteria (Escherichia coli NCTC 5933) and the pathogenic fungi (Candida albicans ATCC 753). The agar media were inoculated with the test organisms and a solution of the tested compound in acetone (1 mg/ml) was placed separa-



(III)

tely in cups (8 mm diameter) in the agar medium. The plates were incubated for 24 hours at 37°C and the resulting zone of growth inhibition was measured. The inhibitory effect of the tested compounds and the antibacterial antibiotic penicillin G. (P.G.) and the antifungal antibiotic mycostatin (M) both in concentration of 100 i.u/ml are shown in table-V.

Experimental

All melting points are uncorrected, IR spectra in KBr were recorded on Pye-Unicam SP 1000 IR spectrophotometer (λ_{max} in cm^{-1}) and PMR in $CDCl_3$ were recorded on Varian EM-390 90 MHz instrument using TMS as reference (Chemical shift in δ ,ppm).

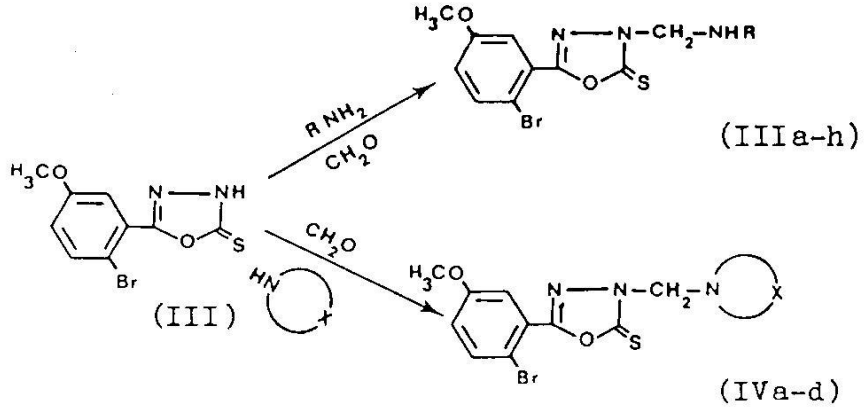
N-Arylidene-2-bromo-5-methoxybenzoylhydrazines (Ia-e)

The appropriate carbonyl compound (0.01 mole) was added to a hot solution of 2-bromo-5-methoxybenzoylhydrazine (0.01 mole) in ethanol (30 ml) and the mixture was heated under reflux for 2 hours. On cooling, the separated solid was filtered, washed with ethanol and crystallized. (Table-I).

2-Substituted-3-acetyl-5-(2-bromo-5-methoxyphenyl)-1,3,4-oxadiazolines (IIa-e)

The appropriate hydrazone (Ia-e); (1 gm) was heated under reflux with acetic anhydride (5 ml) for 30 minutes. On cooling, the mixture was poured onto crushed ice (100 g) and stirred for 20 minutes. The separated solid was washed with water, dried and crystallized (Table-II).

The IR spectrum of compound (IId) exhibited bands at 1650 (C=O), 1600 (C=N), 1260 (C-O-C) and 1510 (NO_2). The PMR spectrum of the same compound displayed signals atδ6.8-7.7 (m, 5H, Ar-H),δ4.4 (s, 1H, oxadiazoline-H),δ3.8 (s, 3H, OCH_3) andδ2.4 (s, 3H, $COCH_3$).



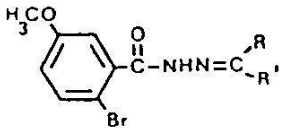
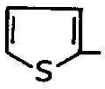
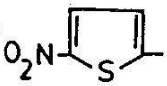
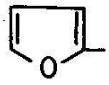
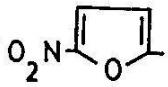
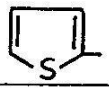


Table-I: N-Arylidene-2-bromo-5-methoxybenzoylhydrazines (Ia-e)

Compd. No.	R	R'	Cryst. Solv.	M.P. °C	Yield %	Formula+
(Ia)		H	Ethanol	191	98	$C_{13}H_{11}BrN_2O_2S$
(Ib)		H	Aqueous-ethanol	214-6	95	$C_{13}H_{10}BrN_3O_4S$
(Ic)		H	Aqueous-ethanol	158	98	$C_{13}H_{11}BrN_2O_3$
(Id)		H	Ethanol	203-5	92	$C_{13}H_{10}BrN_3O_5$
(Ie)		CH_3	Ethanol	188	88	$C_{14}H_{13}BrN_2O_2S$

+Satisfactory elemental analysis was obtained for all compounds.

5-(2-Bromo-5-methoxyphenyl)-1,3,4-oxadiazoline-2-thione (III)

A mixture of 2-bromo-5-methoxybenzoylhydrazine (0.1 mole), potassium hydroxide (0.1 mole) and carbon disulphide (20 ml) in ethanol (20 ml), was heated under reflux until the evolution of hydrogen sulphide had nearly stopped (about 6 hours). The excess solvent was removed by distillation and the residue was dissolved in water (100 ml) and filtered. The clear filtrate was acidified with dilute hydrochloric acid, the precipitated solid was filtered, washed with water, dried and crystallized from ethanol, m.p. 202°C, yield 95%, analysis: Calcd. % C 37.63, H 2.46, S 11.16, Found % C 37.4, H 2.5, S 11.4.

The PMR spectrum of compound (III) exhibited signals at 6.9-7.7 (m, 4H, Ar-H and NH), 4.35 (s, 1H, SH) and 3.85 (s, 3H, OCH_3).

3-Substitutedaminomethyl-5-(2-bromo-5-methoxyphenyl)-1,3,4-oxadiazoline-2-thiones (IIIa-h) and (IVa-d)

To a stirred mixture of 5-(2-bromo-5-methoxyphenyl)-1,3,4-oxdiazoline-5-thione (0.005 mole) and formaldehyde solution (1 ml; 35%) in ethanol (15

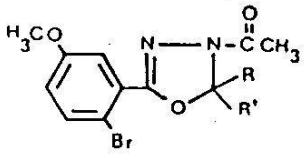
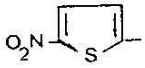
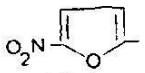


Table-II: 2-Substituted-3-acetyl-5-(2-bromo-5-methoxyphenyl)-1,3,4-oxadiazolines (IIa-e)

Comp. No.	R	R'	Cryst. Solv.	M.P. °C	Yield %	Formula[+]
(IIa)		H	Pet.ether 60-80	118	55	$C_{15}H_{13}BrN_2O_3S$
(IIb)		H	Ethanol	176	50	$C_{15}H_{12}BrN_3O_5S$
(IIc)		H	Aqueous-ethanol	106	55	$C_{15}H_{13}BrN_2O_4$
(IId)		H	Ethanol	157	45	$C_{15}H_{12}BrN_3O_6$
(IIe)		CH_3	Ethanol	152	65	$C_{16}H_{15}BrN_2O_3S$

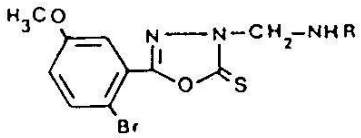


Table-III: 3-Substitutedaminomethyl-5-(2-bromo-5-methoxyphenyl)-1,3,4-oxadiazoline-2-thiones (IIIa-h)

Compd. No.	R	Cryst. Solv.	M.P °C	Yield %	Formula[+]
(IIIa)	C_6H_5-	Aqueous-ethanol	143	95	$C_{16}H_{14}BrN_3O_2S$
(IIIb)	o-ClC_6H_4-	Ethanol	131	90	$C_{16}H_{13}BrClN_3O_2S$
(IIIc)	m-ClC_6H_4-	Ethanol	152	95	$C_{16}H_{13}BrClN_3O_2S$
(IIId)	p-$NO_2C_6H_4$-	Ethanol	218	85	$C_{16}H_{13}BrN_4O_4S$
(IIIe)	p-$OCH_3C_6H_4$-	Aqueous-ethanol	122	90	$C_{17}H_{16}BrN_3O_3S$
(IIIf)	p-$CH_3C_6H_4$-	Pet.Ether 60-80	129	90	$C_{17}H_{16}BrN_3O_2S$
(IIIg)	$C_6H_5CH_2$-	Ethanol	136	95	$C_{17}H_{16}BrN_3O_2S$
(IIIh)	n-C_4H_9-	Pet.Ether 60-80	112	90	$C_{14}H_{18}BrN_3O_2S$

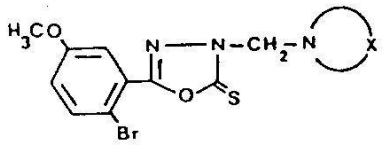


Table-IV: 3-Substitutedaminomethyl-5-(2-bromo-5-methoxyphenyl)-1,3,4-oxadiazoline-2-thiones (IVa-d)

Comp. No.	-N X	Cryst. Solv.	M.P. °C	Yield %	Formula+
(IVa)	-N	Aqueous-ehtnaol	125	88	$C_{15}H_{18}BrN_3O_2S$
(IVb)	-N O	Aqueous-ethanol	121	85	$C_{14}H_{16}BrN_3O_3S$
(IVc)	-N	Pet.Ether 60-80	103	85	$C_{14}H_{16}BrN_3O_2S$
(IVd)	-N N-CH_3	Ethanol	127	85	$C_{15}H_{19}BrN_4O_2S$

Table-V: The Diameter of the Inhibition Zones (mm) exhibited by the compounds (Id), (III), (IIIc), (IIId and IVd) each in concentration of 1 mg/ml and the Antibiotics Penicillin G (P.G.) and Mycostatin (M) each in concentration 100.i.u./ml.

Compd.No.	Staph. aureus	E.coli	C.albicans
(Id)	16	--	12
(III)	--	--	--
(IIIc)	20	--	--
(IIId)	11	--	--
(IVd)	10	--	--
P.G.	17	--	--
M	--	--	18

(--) Inactive.

ml), ethanolic solution of the appropriate amine (0.005 mole) was added gradually over a period of 30 minutes. The mixture was stired for further one hour and refrigerated overnight. The precipitated solid was filtered, washed with aqueous-ethanol, dried and crystallized (Table-III and IV).

The IR spectra of compounds, (IIIa), (IIIc) and (IIIf) exhibited bands at 3100-3300 (NH), 1600 (C=N), 1350-1370 (C=S) and 1260 (C-O-C).

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