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Preparation of 2-(N-substituted carboxamido methyl thio) -5-([4-(4-chloro benzylidine) amino phenyl]-1,3,4- oxadiazoles

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ABSTRACT

1,3,4-Oxadizoles form a biologically important group of compounds having activities like analgesic, anti-inflammatory, bactericidal, antifungal, anticonvulsant, psychotropic, plant growth regulating and mono amino oxidase inhibition. This research has focused on the incorporation of the oxadiazole moiety into isoniazid because of their versatile biological action, to get 2-(N-substituted carboxamido methyl thio) -5-([4-(4-chloro benzylidine) amino phenyl]-1,3,4- oxadiazole to explore the possibilities of some altered biological action. The synthesized compounds were characterized by Melting point, Thin layer chromatographyInfra red, Nuclear magnetic resonance spectroscopy, etc. Almost all the synthesized compounds possessed good activity as compared to the standard.

KEYWORDS

1,3,4-Oxadiazole;
Antibacterial;
Anti-tubercular.

INTRODUCTION

The herbicidal, bactericidal and insecticidal properties exhibited by oxadiazole compounds[1,2] have made them of considerable interest especially in the field of pesticide chemistry.

Hagimoto et al.[3] prepared a mixture of 7% 2,5-disubstituted oxadiazoles, 91.5% bentonite and 1.5% methoxyurea and used 400 g/acre. The mixture was useful to destroy Echinochloa crus – galli, Monochoria vaginalis, Cyperus microiria and Lindernia pyxidaria. Yamamoto et al.[4] prepared 2,4,5-trisubstituted 1,3,4-oxadiazoles and tested their insecticidal activity. Green rice leaphopper (Nephotettix cineticeps) was totally controlled within 24 hrs. by some of these compounds. An effective insecticide based on oxadiazole moiety against house flies and cockroaches was patented[5]. Srivastava et al.[6] have reported some 1,3,4-oxadiazoles as virucidal agents against the plant virus SRV. Goswami et al.[7] have prepared some 3,5-disubstituted 1,3,4-oxadiaxole-2-thiones and screened for their fungitoxic properties against Curvularia verruciformis and Alterneria tenuis. The degree of inhibition ranged from 38-100% for few compounds. Some 3-and 5-substituted 1,3,4-oxadiazol -2-ones have also been reported to exhibit antimycobacterial as well as fungicidal activity[8,9]

Antitubercular activity[10] of some 1,3,4-oxadiazole compounds was also reported. Ram et al.[11] prepared some oxadiazolthiones and tested for anticonvulsant activity. Bhargava et al.[12] have reported some N-substituted -1,3,4-oxadiazoles as potential anticonvulsant compounds. He also pointed out that mono-, di-and tri-methyl substitution in the phenyl ring decreased the

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anticonvulsant activity. Mazzone et al.[13] have synthesised some 2,5 – disubstituted 1,3,4-oxadiazoles and screened for anti-inflammatory, sedative and analgesic activity on rate and mice with satisfactory tresults. Saxena at al.[14] have tested some 1,3,4-oxadiazoles for acetylcholine esterase inhibitory activity on rat brain at three different concentrations. Some of the compounds showed promising results.

This formal a basis for the further study of oxadiazoles as they themselves show pharmacodynamic properties.

Many hydrazine derivatives have been reported as important medicinal compounds. Hydrazide of isonicotinic acid is one of the most effective druge for the treatment of tuberculosis. It has opened a new branch in medicinal chemistry and large number of structurally related compounds have been synthesised and tested for their antimicrobial activity. Large number of carboxy hydrazides have been examined for antitubercular activity[15] Benzoyl hydrazide and ring substituted analogs are active against bovine strain of mycobacteria[16]

Benzocaine is reported to posses different types of biological propertie. Benzocaine has been known to possess marked anaesthetic properties and it is used as a dusting powder on wounds. It is also and in form or ointment[17]. Cinnamic acid salt of benzocaine is highly potent quick local anaesthetic. Clark[18] in a review of benzocaine has described its valuable use in teething lotion, antiseptic toothache drops, earache drops, and vanishing cream for sun and wind burns. Block et al.[19] tested benzocaine and its analogs for their antitubercular action. Benzocaine and other esters of p-amino ben-

REACTION SCHEME

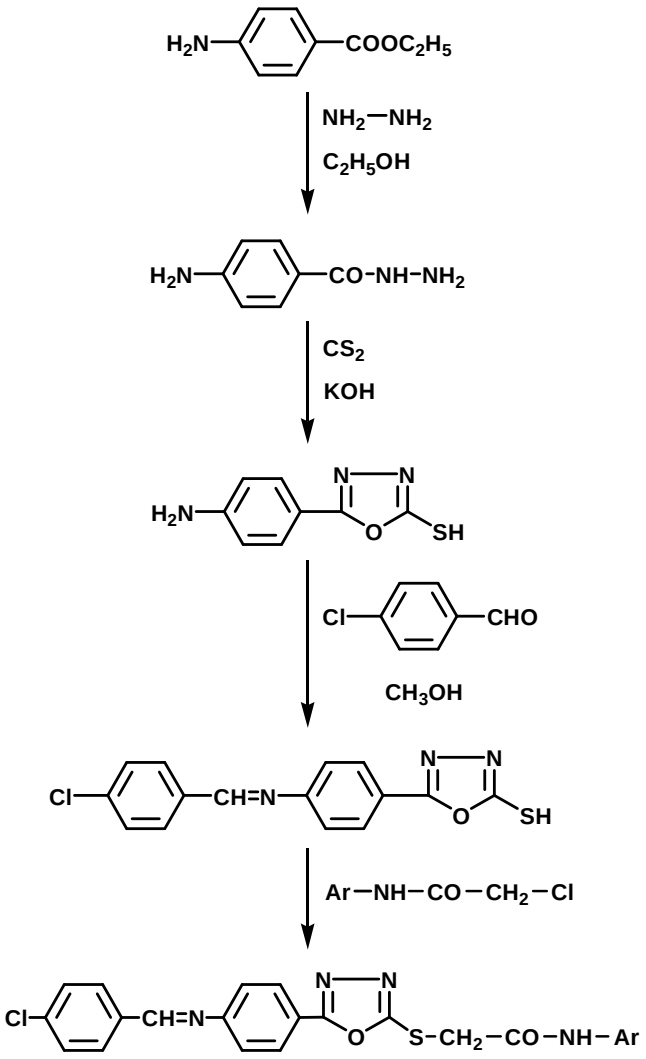

TABLE 1

Sr.No.	R	Molecular Formula	M.V.	Yield %	M.P.°C	% of N		% of S	
						Found	Reqd.	Found	Reqd.
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)
1.	-C_6H_5	$C_{23}H_{17}O_2N_4SCl$	448.5	45	205	12.44	12.48	7.10	7.13
2.	-2-Cl-C_6H_4	$C_{23}H_{16}O_2N_4SCl_2$	483	51	170	11.55	11.59	6.65	6.62
3.	-3-Cl-C_6H_4	$C_{23}H_{16}O_2N_4SCl_2$	483	47	120	11.60	11.59	6.61	6.62
4.									
5.	-2-NO_2-C_6H_4	$C_{23}H_{16}O_4N_5SCl$	493.5	54	175	14.19	14.18	6.45	6.48
6.	-3-NO_2-C_6H_4	$C_{23}H_{16}O_4N_5SC$;	493.5	49	187	14.15	14.18	6.46	6.48
7.	-4-NO_2-C_6H_4	$C_{23}H_{16}O_4N_5SCl$	493.5	48	157	14.20	14.18	6.50	6.48
8.	-2-OC_2H_5-C_6H_4	$C_{25}H_{21}O_3N_3SCl$	492.5	49	155	11.30	11.37	6.43	6.49
9.	-4-OC_2H_5-C_6H_4	$C_{25}H_{21}O_3N_4SCl$	492.5	55	188	11.41	11.37	6.47	6.49
10.	-4-Br-C_6H_4	$C_{23}H_{16}O_2N_4SClBr$	527.5	49	182	10.58	10.61	6.03	6.06

zoic acid are useful in local treatment of painful tuberculosis lesions such as lerygeal tuberculosis[20]. Benzocaine is also used in antiseptic and antibacterial preparations such as "sulfonycaine" which is composed of boric acid, benzocaine and sulfonamide[21]. Hydrazide of pamino benzoic acid is inactive against tubercle bacilli[22] but some of its derivatives are found to be active as antimicrobial agents. Thaker and Parekh[23] have prepared Schiff's bases of p-amino benzoyl hydrazide with various aldehydes and tested for antibacterial and antitubercular activity. Some of them have shown remarkable activity.

From the above observations, we were inspired to synthesise titled compounds-2-(N-phenyl carboxamido methylthio)-5-(4-chloro phenyl benzylidine) -1,3,4, oxadiazoles.

The hydrazide of p-amino benzoic acid was prepared by reaction of benzocaine with hydrazine hydrate in ethanol. Oxadiazole ws prepared by the method described in the first section of Part I. Schiff's bases were prepared by refluxing a mixture of oxadiazole-2-thiones and appropriate aldehyde in ethanol. Finally titled compound were prepared by heating latter with N-chloroacetyl chloride in alkaline alcohol.

EXPERIMENTAL

Chemicals were procured from E. Merck (India) and S. D. Fine Chemicals (India). Melting points were taken in open capillary tubes and are uncorrected. Microanalysis of the compounds was done on a Perkin-Elmer model 240 analyzer (Perkin-Elmer, USA) and the values were found within ± 0.4 % of the theoretical values. IR (KBr) spectra were recorded on a Perkin-Elmer 157 infrared spectrometer (*n*max in cm–1) (Perkin-Elmer, USA) and 1H NMR spectra were recorded on a Varian E-360 MHz (Perkin-Elmer, USA) or Bruker spectrometer DPX-300MHz (Bruker, Germany) with tetramethylsilane (TMS) as an internal standard. Mass spectra were recorded on a Jeol JMS-D 300 instrument (Jeol, Japan) fitted with a JMS 2000 data system at 70 eV. Spectral data are consistent with the assigned structures. The progress of the reactions was monitored on silica gel G plates using iodine vapour as visualizing agent. All solvents were distilled prior to use.

Preparation of p-amino benzoyl hydrazine

Benzocaine (33.0 g, 0.2 mole) was dissolved in ethanol (70ml, 95%) with stirring. Hydrazine hydrate (80ml, 99%) was added dropwise and contents were refluxed on waterbath for four hours. Excess of solvent was distilled off and the reaction mixture was cooled to 4-5 ^{o} C. The separated product was filtered, washed with chilled ethanol and dried in oven at 105^{o} C. Recrystallised from ethanol. Yield, 23.5 g; 78%, m.p. 209-10 ^{o} C; Found: N, 27.78%, $C_7H_9N_3O$; Required: N, 27.81%

Preparation of 5-(4-amino phenyl)-1,3,4-oxadiazol-2-thione

p-Amino benzoyl hydrazine (15.1 g, 0.1 mole) ws dissolved in solution of potassium hydroxide (5.6 g; 0.1 mole) in 100 ml water with constant stirring. Methanol (100 ml) was added dropwise and a clear solution was obtained. CS2(6ml, 0.1 mole) was added dropwise with constant stirring. The resulting solution was refluxed for six hours and then concentrated. Residual solution was poured in water and filtered. The filtrate was acidified with dilute HCl. The product thus obtained ws filtered washed with water and dried. Recrystallised from ethanol. Yield, 16.51 g; 86 %, m.p. 259-10 ^{o} C; Found: N, 21.80%; S 16.60%, C_8H_7 ON_3S; Required: N, 21.87% S 16.66%

Preparation of 5-[4-(4-chloro benzylidin)-amino] – phenyl 1,3,4-oxadiazole -2-thione

5-(4-Amino phenyl)-1,3,4-oxadiazole – 2 – thione (19.2 g; 0.1 mole) was dissolved in spirit. p-chloro benzaldehyde (14.05g ; 0.1 mole) was added dropwise with constant strring. Resultant solution was refluxed on a waterbath for three hours. Excess of solvent was distilled off. The contents were allowed to cool at room temperature. The separated product was filtered, washed with water and dried. Recrystallized from ethanol. Yield, 25.25 g; 81 %, m.p. 156 ^{o} C; Found: N, 13.26%; S 10.09%, $C_{15}H_{10}$ ON_3SCl; Required: N, 13.31% S 10.14%

Preparation of 2-(N-phenyl carboxamido methl thio) -5-(4-(chloro benzylidine) amino] – phenyl-1,3,4- oxadiazole

5-[4-(4-chloro benzylidin) –amno) –phenyl 1,3,4-

oxadiazol-2-thione (3.15 g. 0.01 mole) was dissolved in solution of potassium hydroxide (5 g) in water (20 ml). α- Chloro acetanilide (2.37 g; 0.014 mole) was added with constant stirring at 80° C. Stirring was continued and the reaction mixture maintained at 80° C for two hours.

The contents were left overnight. The crystals were filtered. washed with water and dried. Recystallised from ethanol. Yield, 2.016 g; 45 %, m.p. 205° C; Found: N, 12.44%; S 7.10%, $C_{23}H_{17}O_2N_4SCl$; Required: N, 12.48% S 7.13%

Spectral data: The IR spectra of 2-(N-Pheryl carboxamido methylthio)-5-[4-chloro benzylidine) amino phenyl]-1,3,4 –oxadiazole showed following characteristic bands. 3310 cm^{-1} (-NH str., acetamido group), 1725 cm^{-1}(>C=O str. Acyclic) 1650 cm^{-1} (-CO-NH linkage), 1600 cm^{-1} (>C=N- str. Cyclic), 1520 cm^{-1} (C-O-C str. Cyclic), 1400 cm^{-1} (S-CH2 str.) 1280 cm^{-1} (= N-N=C str., cyclic str.) 820 cm^{-1} (C-H bending for 1,4 – disubstituted benzene ring), 690 cm^{-1} (C-H bending, mono substituted benzene ring), 770 cm^{-1} (C-Cl str. For benzene substitution.) PMR spectrum of the compound showed signals as followes: 9.5 δ (broad signal due to -NH proton), 6.8-7.3δ (multiplet aromatic protons), 1.94δ (singlet, Ar- CH – Str.), 2.9 δ (-CH2 singlet.)

CONCLUSIONS

A new class of oxadiazoles was synthesized by cyclization of the terminal carboxylic group of an aroyl propionic acid with the objective to develop better anti-inflammatory and analgesic molecules with or without ulcerogenic activity. The results of biological tests make novel oxadiazoles interesting lead molecules for further synthetic and biological evaluation. It can be concluded that this class of compounds certainly hold great promise for discovering safer anti-inflammatory agents.

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