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Synthesis of series of 2-methyl-4-(substituted phenyl)-1,5-benzodiazepines and evaluation of antibacterial activity

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ABSTRACT

A series of 2-methyl-4-(halogeno substituted phenyl)-1,5-benzodiazepines were synthesized and studied for antibacterial activity. Some of the compound showed significant inhibition to growth of bacteria.

Keywords: 1,5-benzodiazepines, synthesis and antimicrobial activity.

INTRODUCTION

Heterocyclic compounds are often considered privileged structure in medicinal chemistry [1,2] due to their biological effects. Benzodiazepines are important class of compounds used as a drugs having effect on central nervous system, for example, clozapine, olanzapine, and quetiapine are used in the clinic for treating schizophrenia, while clonazepam, diazepam, lorazepam, nitrazepam and oxazepam are used as antianxiety drugs.

Clobazam, a 1,5-benzodiazepine has displayed anticonvulsant action in a variety of experimental models. Compared to 1,4-benzodiazepine, clobazam appears to have a lower incidence of side effects and greater antiepileptic effects, but no double-blind controlled clinical studies of clobazam with other antiepileptic drugs have been undertaken. Clobazam is effective against generalized tonic-clonic and partial seizures. A major limitation to its long-term use is the development of tolerance. Clobazam is used as adjunctive treatment with other standard anticonvulsant drugs in patients with intractable seizures. Clobazam has been marketed primarily

as an anxolytic agent, but it has also been approved for antiepileptic indication by several health authorities, including those in the United Kingdom and Germany.

In addition, there are number of reports of heterocyclic scaffolds containing the benzodiazepine moiety, which show additional biological activities [1,2,3]. Benzodiazepine derivatives also find commercial use in photograph [4] and also as anti-inflammatory agents [5]. A number of 1,5-benzodiazepine such as: 2,4-diphenyl-1,5-benzodiazepine, 7-amino-2,4-dimethyl-1,5-benzodiazepine, 7-nitro-2,4-dimethyl-1,5-benzodiazepine, and 7-bis-(2-chloro-ethyl)-amino-2,4-dimethyl-1,5-benzodiazepine have been reported to possess cancerostatic activity [6].

In spite of their use in pharmaceutical, industrial and synthetic point of view, only two methods are widely used for synthesis. Methods include condensation of *o*-phenylenediamine with (1) α, β-unsaturated carbonyl compound and (2) β-diketones or ketones in the presence of different catalyst.

We here report the synthesis of 1,5-benzodizepines from *o*-phenylenediamine and halogenohydroxy substituted β-diketones using ethanol as solvent medium. Method is simple, easy work up, good yield, pure crystalline product separated out within 15-35 min.

EXPERIMENTAL SECTION

All melting points were determined in open capillary and are uncorrected. The IR spectra were recorded on Perkin-Elmer 157 and Shimadzu spectrometer. ^{1}H NMR was recorded on Aveanue-300 and Brucker WM 400 FT MH_Z instrument using TMS as internal standard. The reactions were monitored on TLC and the spots were located in iodine chamber.

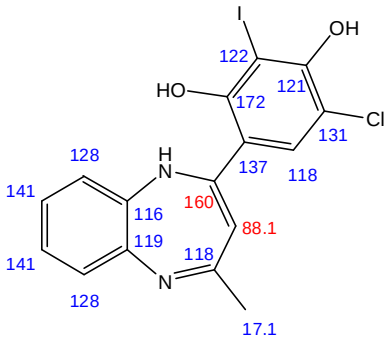
General Procedure for Synthesis of 2-methyl-4-(substituted phenyl)-1,5-benzodiazepines
A mixture of *o*-phenylenediamine (0.01 mol), β-diketone (0.01 mol) were dissolved in methanol (15 ml) and two drops of acetic acid was added. Reaction mixture was refluxed on boiling water bath for 15-35 min. Half of the solvent was evaporated and cooled the solution to room temperature. Solid separated out. Solid was filtered washed with water and crystallized from ethanol. Yield, M.P. and analytical data is represented in Table **1**.

Spectral Data for Some 1,5-Benzodiazepines
2-methyl-4-[(2', 4'-dihydroxy-3,5-diiodophenyl)]-1,5-benzodiazepine
IR νmax cm^{-1}: 3428 (OH), 3348 (NH), 1620 (C=N), 1591, 1494 (C=C Aromatic), 3061 (=CH)
^{1}H NMR : δ 2.38 (s, 3H, CH_3), 3.84 (s, 1H, NH), 6.70-7.84 (m, 5H, ArH and =CH)
MS: m/z : M^+ 518, 504, 482, 464, 431,362,294,152,103, 77, 63.

2-methyl-4-[(2', 4'-dihydroxy-3,5-dibromo phenyl)]-1,5-benzodiazepine
IR νmax cm^{-1}: 3427 (OH), 3347 (NH), 1590 (C=N), 1519, 1494, 1457 (C=C Aromatic)
^{1}H NMR : δ2.37 (s, 3H, CH_3), 3.68 (s, 1H, NH), 6.77-7.76 (m, 5H, ArH and =CH), 17.05 (s, 1H, OH)

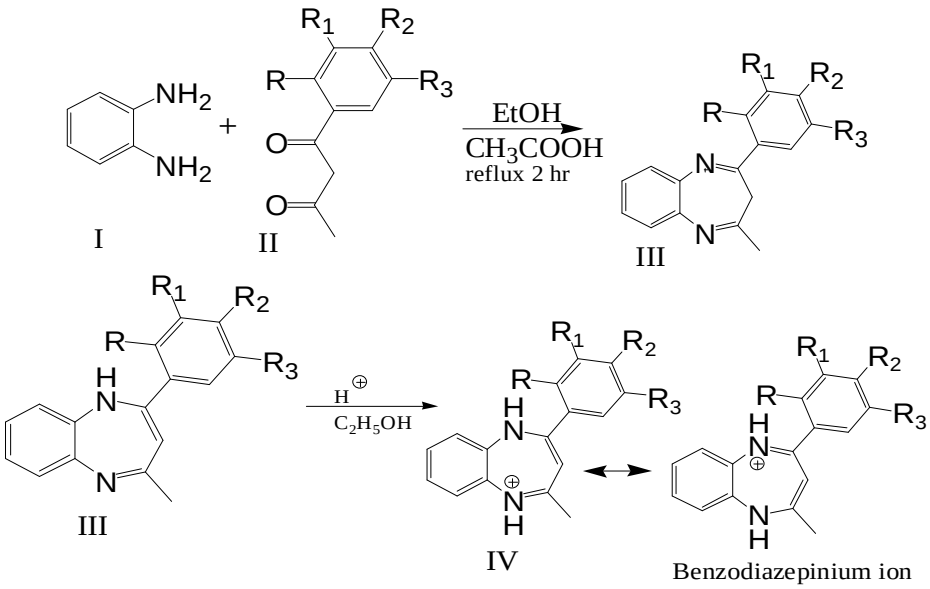
2-methyl-4-[(2', 4'-dihydroxy-3'-iodo-5'-chlorophenyl)]-1,5-benzodiazepine
^{1}H NMR : δ 2.35 (s, 3H, CH_3), 4.97(s, 1H, NH), 6.61-7.93(m, 7H, ArH and =CH)

^{13}C NMR:



Number of carbon atoms in this compound are 16. This compound has two sets equivalent carbon, 2',6'- and 3',5'-.This compound shows fourteen peaks. Peak at 17.12 is due to aliphatic (methyl) carbon and a peak at 84.5 due to –CH=C-, a peak at 118 is due to =C-CH_3 and remaining peaks 116, 119, 121.8, 122, 127, 128.60, 131, 137.9, 141.46, 160.4, 172.2 are in aromatic region.

Scheme I: Synthesis of Some New Substituted 1,5-Benzodiazepines



Scheme I

Entry:	R	R_1	R_2	R_3
1.	OCH_3	I	H	I
2.	OH	Cl	H	Cl
3.	H	CH_3	OH	I
4.	OH	I	H	Cl
5.	OH	I	H	I
6.	OH	Br	H	CH_3
7.	OH	Br	H	Cl
8.	OH	Br	OH	Br
9.	OH	I	OH	I
10.	OH	Cl	OH	Cl

RESULTS AND DISCUSSION

Equimolar quantities of *o*–phenylenediamine and 1-(substituted phenyl)-3-methyl propane 1,3-dione were dissolved in methanol (15 ml), 2 drops of glacial acetic acid was added and reaction mixture was refluxed on water bath for 15-35 min. Half of the solvent was evaporated and then on cooling the solution up to room temperature, solid separated. Solid was filtered, washed with water and crystallized from ethanol in excellent yield (Scheme I, Table I). Purity of the compounds was checked by TLC. Structures of the compounds were confirmed by spectral data and elemental analysis. All the benzodiazepines prepared are pale yellow to orange in color and crystalline. Structures of these 1,5-benzodiazepines were also confirmed by violet coloration with hydrochloric acid. 1,5-Benzodiazepine dissolved in ethanol on treating with dilute hydrochloric acid gives violet coloration, a characteristic property of 1,5-benzodizepines. Violet coloration is believed to be due the formation benzodiazepinium ion.

Infra red spectra of the 1,5-benzodiazepines showed characteristic bands at 3300 cm^{-1} due to N-H stretching at 1620-1600 cm-1 due to C=N stretching, near at 1600-1500 cm^{-1} due to aromatic stretching, a band in between 1590-1570 cm^{-1} due to N-H out of plane bending vibrations. The observation of the bands due to N-H stretching vibrations indicate that 1,5-benzodiazepines can be represented by the imine structure (IV). In ^{1}HNMR a characteristic singlet peak appears near at δ 6.5 is due to =CH. Therefore synthesis of 1,5-benzodiazepines by condensation of *o*-phenylenediamine with β-diketones is easier as compared to synthesis using chalcones and ketones.

Table 1: Physical and Analytical data of Some New Substituted 1,5-Benzodiazepines

Compound	M.P. (°C)	Yield (%)	Elemental Analysis % Found (Calculated)				Zone of Inhibition(mm)			
			C	H	N	X (Cl, Br, I)	Bs	Ec	E.coli	Xc.
1	170	74	39.03 (39.56)	2.14 (2.73)	5.00 (5.43)	48.88 (49.18)	13	18	12	20
2	168	70	60.25 (60.21)	3.78 (3.79)	8.52 (8.78)	21.85 (22.21)	19	23	26	35
3	215	72	37.97 (38.27)	2.01 (2.41)	5.40 (5.58)	50.12 (50.55)	10	09	11	14
4	158	73	46.08 (46.80)	2.99 (2.95)	7.15 (6.82)	39.86 (39.53)	16	20	12	15
5	160	75	37.97 (38.27)	2.01 (2.41)	5.30 (5.58)	50.21 (50.55)	17	22	23	28
6	112	71	58.94 (59.49)	4.56 (4.41)	8.42 (8.16)	23.68 (23.28)	11	12	09	17
7	165	74	52.08 (52.85)	3.31 (3.33)	8.82 (7.70)	32.15 (31.72)	08	12	10	13
8	168	74	45.13 (45.31)	2.81 (2.85)	6.23 (6.61)	37.41 (37.68)	12	10	09	14
9	132	73	36.56 (37.09)	1.86 (2.33)	5.87 (5.41)	49.44 (48.99)	10	15	09	18
10	153	71	60.54 (60.21)	3.76 (3.79)	8.75 (8.78)	21.65 (21.15)	16	18	29	34
Ampicillin							**18**	**20**	**23**	**25**

** Crystal appearances of all the compounds is pale Yellow to Orange.*

Antimicrobial Activity

Synthesized 1,5-benzodiazepines were tested for their antibacterial against Escherichia coli (E. coli), Bacillus subtilis (Bs), Xanthomonas citri (Xc) and Ervinia carotovara (Ec). Disc diffusion method was employed for bacterial activity study measuring diameter of zone of inhibition in mm. The compound **1**, **4**, **5** and **10** show good inhibitory growth against different bacteria.

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