RESEARCH PAPER

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Synthesis and Biological Activities of Some 2-Aryloxymethyl-4-(2Hydroxyphenyl)-1,5-Benzodiazepines

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2-Aryloxymethyl-4-(2-hydroxyphenyl)-1,5-benzoliazepines have been synthesised by the cyclocondensation of 1,3-diketone with O- phenylenediamine and screened for their fungicidal, herbicidal and cardiovascular activities.

THE SEDATIVE, tranquilizing, analgesic, antipyretic, anticonvulsant, antihypertensive and anti-inflamatory activities of 1,5-benzodiazepines are well documented.[1-4] However, only few attempts have been made so far to determine the pesticidal properties[5] of this rig. Therefore, it appeared interesting to synthesise 1,5-benzodiazepines having aryloxy moiety which forms the structural unit of some well known pesticidal agents including herbicidal aryloxy and heteroaryloxy alkanoic acids[6,7] to evaluate their biocidal activities.

The required 2-(aryloxy acetoxy) acetophenones(I) have been prepared by the esterification of aryloxyacetic acid with 2-hydroxyacetophenone in presence of pyridine and $POCl_3$, was subjected to B.V. Transformation to give w-substituted aryloxyaceto-2-hydroxy acetophenones(II). The cyclocondensation of compounds (II) with-o-phenylenediamine furnished the title compounds (III).

The structure of these products have been established by elemental analyses and spectral data.

EXPERIMENTAL

Melting points were taken in open capillaries and are uncorrected. IR spectra were recorded on Perkin-Elmer 157 spectrophotometer in KBr disc (vmax in cm^{-1}) and H^1NMR spectra were recorded on a Varian EM-360 (60 MHz) spectrometer (chemical shifts in δ) in DMSO-d_6.

2-(Phenoxyacetoxy) acetophenone (Ia):

A mixture of phenoxyacetic acid (0.01 M) and 2- hydroxyacetophenone (0.01 M) was dissolved in pyridine (60 ml) and $POCl_3$ (25 ml) was added dropwise with continuous stirring in cold. The resulting mixture was left for 4-hrs at room temperature, On acidification, solid mass of 2- (phenoxyacetoxy) acetophenone was separated out which was filtered, washed dried and recrystallised from aqueous ethanol. M.P. 73°C, Yield 64%.

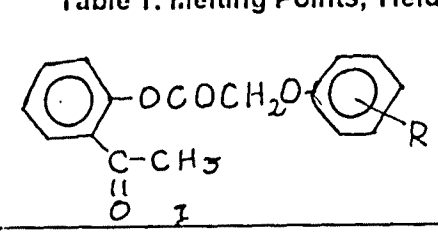
IR(KBr) ν^{cm-1}max : 2910 (OCH_2), 1750 (O-C-CH_2-), 1720(-C-CH_3), 1590, 1480, 1420 (Aromatic ring), 1260 (C–O–C) PMR (DMSO-d_6) δ 2.5 (s,3H, CH_3), 4.5(s,2H, OCH_2), 6.9-7.5 (m, 9H, ArH).

Similarly other compounds were prepared and are recorded in table 1.

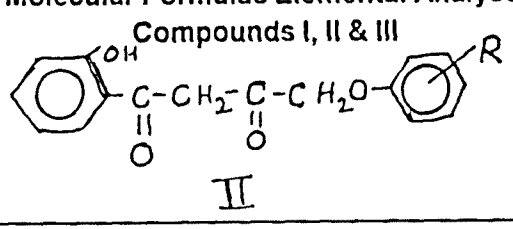
w-(Pheynoxyaceto) 2-hydroxyacetophenone (IIa)

The powdered KOH (0.02 M) and pyridine (5 ml) was stirred in a beaker and then 2-(phenoxyacetoxy)

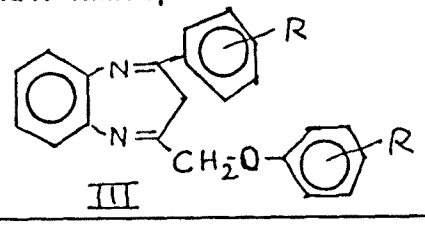
Table 1: Melting Points, Yield, Molecular Formulas Elemental Analyses and H^1 NMR spectral data of Compounds I, II & III



I



II



III

Compd.	R	M.P. C°	Yield %	Molecular formula	Analyses % Found(Calcd) of C	H	N	H^1 NMR (DMS-d_6) δ
Ia	H	73	64	$C_{16}H_{14}O_4$	71.20(17.11)	5.10(5.18)	—	2.5(s,3H,CH_3), 4.5(s,2H, OCH_2), 6.9-7.5(m,9H,Ar,H)
Ib	2-CH_3	60	69	$C_{17}H_{16}O_4$	71.75(71.83)	5.54(5.63)	—	2.2(s,3H,CH_3), 2.6(s,3H, CH_3), 4.7(s,2H,OCH_2) 7.0-7.6(m, 8H, Ar, H)
Ic	3-CH_3	120	60	$C_{17}H_{16}O_4$	71.88(71.83)	5.70(5.63)	—	—
Id	4-CH_3	110	80	$C_{17}H_{16}O_4$	71.95(71.83)	5.52(5.63)	—	2.2(s,3H,CH_3), 2.6(s,3H CH_3), 4.7(s,2H,OCH_2), 7.0-7.6(m. 8H, Ar H)
Ie	2-Cl	125	74	$C_{16}H_{13}O_4Cl$	62.95(63.05)	4.39(4.27)	—	2.5(s,3H,CH_3), 4.7(s,2H, OCH_2), 7.0-7.7(m,8H,Ar H)
If	4-Cl	113	68	$C_{16}H_{13}O_4Cl$	63.17(63.05)	4.23(4.27)	—	2.6(s,3H,CH_3), 4.6(s,2H, OCH_2), 7.0-7.7(m,8H,Ar H)
Ig	3-CH_3-4-Cl	80	64	$C_{17}H_{15}O_4Cl$	64.20(64.05)	4.79(4.71)	—	2.3(s,3H,CH_3), 2.6(s,3H, CH_3), 4.7(s,2H,OCH_2) 7.0-7.6 (m,7H,Ar H)
Ih	2,4-Cl_2	75	62	$C_{16}H_{12}O_4Cl_2$	56.57(56.64)	3.46(3.54)	—	—
IIa	H	liq.	64	$C_{16}H_{14}O_4$	71.19(71.11)	5.23(5.18)	—	4.7(s,2H,OCH_2), 5.5(s,2H, CH_2), 6.9-7.4(m,9H,Ar H) 8.4(b, 1H, OH)
IIb	2-CH_3	120	58	$C_{17}H_{16}O_4$	71.72(71.83)	5.71(5.63)	—	2.2(s, 3H,CH_3), 4.7(s,2H, OCH_2), 5.7(s,2H,CH_2) 6.9-7.5(m,8H, Ar, H), 8.6(b, 1H OH)
IIc	3-CH_3	liq.	63	$C_{17}H_{16}O_4$	71.70(71.83)	5.51(5.63)	—	—

Compd.	R	M.P. C°	Yield %	Molecular formula	Analyses % Found(Calcd) of C	H	N	H^1 NMR (DMS-d_6) δ
IId	4-CH_3	139	62	$C_{17}H_{16}O_4$	71.91(71.83)	5.54(5.63)	—	2.3(s,3H,CH_3), 4.8(s,2H, OCH_2), 5.6(s,2H,CH_2) 6.9-7.5(m,8H, ArH) 8.6(b, 1H, OH)
IIe	2-Cl	142	69	$C_{16}H_{13}O_4Cl$	63.14(63.05)	4.34(4.27)	—	4.8(s,2H,OCH_2),5.5(s,2H, CH_2), 6.9-7.4)m,8H, ArH) 8.5(b, 1H, OH).
IIf	4-Cl	128	65	$C_{61}H_{13}O_4Cl$	63.11(63.05)	4.22(4.27)	—	4.8(s,2H,OCH_2), 5.6(s, 2H, CH_2), 7.0-7.6(m, 8H, ArH) 8.6(b, 1H, OH).
IIg	3-CH_3-4-Cl	152	57	$C_{17}H_{15}O_4Cl$	64.19(64.05)	4.82(4.71)	—	2.3(s,3H,CH_3), 4.7(s, 2H, OCH_2), 5.5(s,2H,CH_2) 7.0-7.6(m,7H,ArH) 8.4(b, 1H,OH)
IIh	2,4-Cl_2	125	59	$C_{16}H_{12}O_4Cl_2$	56.76(56.64)	3.63(3.54)	—	—
IIIa	H	90	63	$C_{22}H_{18}N_2O_2$	77.25(77.19)	5.39(5.26)	8.23(8.19)	4.2(s,2H,CH_2, 4.6(s,2H,OCH_2) 6.6-7.6(m,15H,Ar H & 1H, OH)
IIIb	2-CH_3	72	62	$C_{23}H_{20}N_2O_2$	77.60(77.53)	5.73(5.62)	7.7+(7.86)	2.3 (s,3H,CH_3),4.2(s,2H,CH_2) 4.6(s,2H,OCH_2),6.7-7.7(m, 15H, Ar H & 1H, OH)
IIIc	3-CH_3	99	59	$C_{23}H_{20}N_2O_2$	77.63(77.53)	5.76(5.62)	7.92(7.86)	—
IIId	4-CH_3	139	60	$C_{23}H_{20}N_2O_2$	77.44(77.53)	5.69(5.62)	7.97(7.86)	2.3(s,3H,CH_3), 4.3(s,2H,CH_2 4.7(s,2H,OCH_2),6.8-7.7 (m,15H,Ar H & 1H, OH)
IIIe	2-Cl	97	64	$C_{22}H_{17}N_2O_2Cl$	70.21(70.12)	4.44(4.51)	7.0(7.44)	4.3(s,2H,CH_2),4.7(s,2H,OCH_2) 6.8-7.7(m,15H,Ar, H & 1H,OH)
IIIf	4-Cl	90	65	$C_{22}H_{17}N_2O_2Cl$	70.01(70.12)	4.46(4.51)	4.39(7.44)	4.2(s,2H,CH_2),4.7(s,2H,OCH_2) 6.7-7.9(m,15H,ArH & 1H, OH)
IIIg	3-CH_3-4-Cl	100	67	$C_{23}H_{19}N_2O_2Cl$	70.77(70.68)	4.91(4.87)	7.30(7.17)	2.3(s,3H,CH_3),4.2(s,2H,CH_2) 4.6(s,2H,OCH_2)6.7-7.7 (m,14H, ArH & 1H, OH)
IIIh	2,4-Cl_2	35	69	$C_{22}H_{16}N_2O_2Cl_2$	61.33(64.23)	3.79(3.89)	6.89(6.81)	—

acetophenone (0.01 M) was added to it. The mixture was thoroughly rubbed with a glass rod for 1/2 hr with occassional warming. After cooling the reaction mixture, it was poured into ice-cold water containing HCl. The reaction product thus obtained, separated as liquid, washed and dried, Yield 64%.

IR(KBr) ν_{cm-1}max : 3480(OH), 2910, 2840 (aliphatic CH), 1740 (β-diketone), 1590, 1490, 1450 (Aromatic ring), PMR(DMSO-d_6)δ: 4.7 (s, 2H, OCH_2), 5.5(s, 2H, CH_2) 6.9-7.4 (m, 9H, ArH), 8.4(b, 1H, OH)

Similarly other compounds were prepared and are recorded in table 1.

2-Phenoxymethyl-4-(2-hydroxyphenyl)-1,5-benzodiazepine(IIIa)

A mixture of w-(Phenoxyaceto)-2-hydroxyacetophenone (0.01 M) and O-phenylene diamine (0.01 M) was refluxed in methanol for 4 hrs on a water bath. The excess of methanol was distilled off, poured into crushed ice, fine crystals were separated out which were filtered and recrystallised from aqueous ethanol.

M.P. 90°C, Yield 63%.

IR(KBr) ν^{cm-1}_{max} : 3430(OH), 1630(C=N), 1600, 1490 (aromatic ring). PMR (DMSO-d_6) δ: 4.2(s, 2H, CH_2), 4.6 (s, 2H, OCH_2), 6.6-7.6 (m, 15H, ArH & 1H OH).

Similarly other compounds were prepared and are recorded in table 1.

BIOLOGICAL ACTIVITIES

Fungicidal Activity

The fungicidal activity of each compound was evaluated by agar growth technique against three test fungi which are as follows: **Aspergillus niger, Aspergillus flavus and Helminthospeorium oryzae** at 500, 100 and 10 PPM concentrations. A commercial fungicide Dithane M-45 was also tested under similar conditions for comparison. The fungicidal activity displayed by these compounds is recorded in **table 2.**

Herbicidal Activity

The herbicidal activity of each compound was tested for their pre- and post-imergent treatment against four species which include Barnyard grass **(Echinocholeo crusgalli)**, Velvet leaf **(Abuliton theophrashi)** Foxtail green **(Sertaria irridis)** and Johnson grass **(Sorghum helepense)**. The host plant is wheat **(Triticum aestivum)** and application rate 50 Kg/ha. For pre- imergence treatment, the seeds are planted and soil is sprayed with a solution of test chemicals. Test results are observed 10- 14 days after treatment, the test chemicals are sprayed on to 10- 14 days old plants. Test results are observed 8-10 days after treatment and are recorded in **table 3.**

Cardiovascular Screening

Only five compounds have been screened on the cardiovascular system for the positive inotropic activity using the guinea pig left atrium. Isoproterenol was also tested under similar conditions for comparison.

The positive inotropic effects using the electrically stimulated guinea pig left atria, bathed in physiological salt solution containing one-third normal calcium concentration at 32°C was measured and recorded in **table 4.**

RESULTS AND DISCUSSION

The fungicidal data of the tested compounds showed that they are moderately active at 100 ppm concentration against the test fungi and their toxicity

Table 2: Fungicidal Activity of Compounds IIIa-h

Compd. No.	R	Mean % Inihibition after 7 days against Aspergillus niger		Apsergillus flavus		Helminth orv-osporium	orv-ase
		100ppm	10ppm	100ppm	10ppm	100ppm	10ppm
IIIa	H[1]	62	48	69	57	60	46
IIIb	2-CH_3	61	50	54	25	59	34
IIIc	3-CH_3	65	54	65	44	64	45
IIId	4-CH_3	66	54	64	45	64	51
IIIe	2-Cl	67	45	68	42	60	45
IIIf	4-Cl	73	55	75	50	64	59
IIIg	3-CH_3-4-Cl	66	42	65	49	59	51
IIIh	2,4-Cl_2	68	56	56	47	64	57
Dithane	M-45	86	81	92	83	94	81

Table 3: Herbicidal Activity of Compounds IIIa-h

Comp. No.	R	Pre-emergent Herbicidal Activity Test species used				Post-emergent Herbicidal activity Test species used			
	—	Barnyard grass	Velvet leaf	Foxtail green	Johnson grass	Barnyard grass	Velvet leaf	Foxtail green	Johnson grass
IIIa	H	0	1	1	0	0	0.5	0.5	0
IIIb	2-CH_3	0	1	1	1	0	0	0	1
IIIe	3-CH_3	2	3	2	4	2.0	2.5	1	3.5
IIId	4-CH_3	1	2	1	0	0	1	0	0
IIIe	2-Cl	2	1	1	1	1.5	1	0	0.5
IIIf	4-Cl	3	2	2	3	3.0	1	1	2.5
IIIg	4-Cl-3-CH_3	3	3	4	4.5	2.5	2.0	4	3.5
IIIh	2,4-Cl_2	4.5	2.5	2	3.5	3.5	1.5	0.5	2.5

*Phytotoxicity rating (0: 0-30% growth inhibition, 1: 31-50%, 2: 51-70%, 3: 71-80%, 4: 81-90%, 5: 91-100%).

Dose 50Kg/ha.

Table4: Cardiovasuclar Screening of Compounds III

Compound No.	R	Guinea pig left atria positive inotropic activity % increase (Mean ± SD)
IIIa	H	20±8
IIIc	3-CH_3	50 ± 6
IIId	4-CH_3	40 ± 8
IIIg	3-CH_3-4-Cl	60 ± 8
IIIh	2,4-Cl_2	50 ± 10
	Isoproterenol	135 ± 15

decreased considerably upon dilution. 4- Position substitution imparts better fungicidal activity than the 2- or 3-substituted ones at aryloxy moiety.

The herbicidal data of the tested compounds showed the effect of substitution at aryloxy moiety on heterocyclic ring. In regard to the introduction of a chloro atom or methyl group, the 4-position substitution for chloro atom (IIIf) or 3-position substitution for CH_3 group (IIIc) at aryloxy moiety developed better herbicidal activity compared with same atom or group at different position in the same ring. The compounds having 2,4-Cl_2 or 3-CH_3-4- Cl atoms / groups at aryloxy methyl moiety on 2-position of 1,5-benzodiazepine ring are most active compounds of this series probably due to larger group.

Only five compounds were tested for their cardiovascular activity in the guinea pig and the results were compared with isoproterenol. None of the compounds showed promising activity. The most active compound of this series is IIIg.

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REFERENCES

1. Alhadegg M., **Med. Actual.** 1977, 13, 521-7; **Chem. Abstr.** 1978, 88, 163539p.
2. Tamura, T., **Jpn Kokai Tokkyo Koho** 8102 984 1981; **Chem. Abstr.** 1981, 94, 175182d.
3. Atwal K., **U.S.** US 4650797 1987: **Chem. Abstr.** 1987, 107, 77843n.
4. Mendelson W.B., Paul S.M., Skolnick P., **Pharmacol. Benzodiazepines. Proc. Conf.** 1982, 375 ; **Chem. Abstr.** 1984, 101, 83852g.
5. Clifford D.P., Jackson D., Edwards R.V., Jeffery P., **Pestic Sci.**, 1979, 7, 453 : **Chem. Abstr.**, 1977, 87, 146947g.

6. Troxzelli H., **Weeds Weed Control** 1986, 27, 65, **Chem. Abstr.** 1987, 107, 128980g.

7. Yanai T., Honma T., **Jpn Kokai Tokkyo Koho JP** 61118304 1986: **Chem. Abstr.** 1987, 106, 115243f.

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