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Synthesis and Antifungal Activity of some New 2-Methoxy-4-(N-Substituted Arylidino)Phenoxy Acetic Acid Hydrazides and Their N-Benzylidine Derivatives

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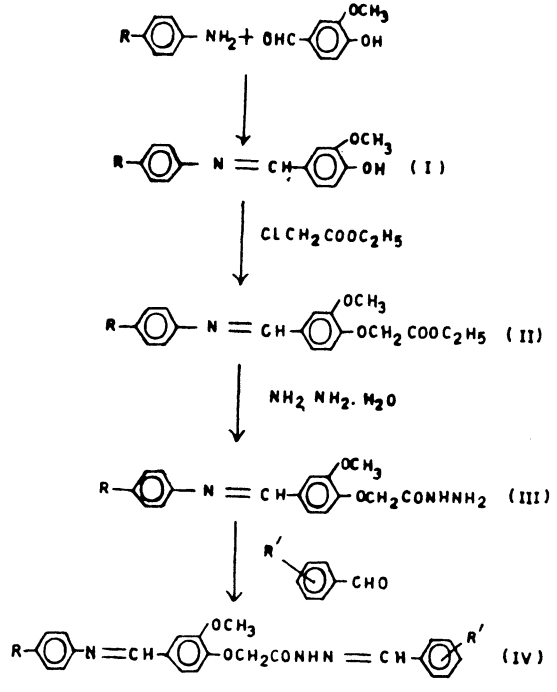
Some 2-methoxy-4-(N-substituted arylidino)phenoxy acetic acid hydrazides and their N-benzylidine derivatives were synthesised and screened for their antifungal activity against *Alternaria alternata, Aspergillus flavus* and *Fusarium moniliforme.*

INTRODUCTION

A large number of hydrazides and hydrazones have been tested as antibacterial, antiviral and antitubercular agents[1-5]. Isonicotinic acid hydrazide and its derivatives are well known for their antitubercular activity[6]. Salicylic acid hydrazide is known to possess antitubercular[7] and fungistatic[8] activities. On the other hand, Schiff's bases are well known to possess promising biological activities[9,10]. In view of the above observations it was considered worthwhile to synthesise some 2-methoxy-4-(N-substituted arylidino)phenoxy acetic acid hydrazides. These hydrazides were further condensed with aryl aldehydes to obtain their N-benzylidine derivatives. These compounds consist of two azomethine linkages and

SCHEME-1



thus their biological activity may be expected to be enhanced. The steps involved in the synthesis are sketched in Scheme I. All these hydrazides and their N-benzylidine derivatives were screened for their antifungal activity against *Alternaria alternata, Aspergillus flavus* and *Fusarium moniliforme* as the test fungi.

EXPERIMENTAL

All melting points were taken in open capillary tubes in H_2SO_4-bath and are uncorrected. Infrared spectra were determined in KBr pellets on Perkin-Elmer infrared spectrophotometer (ν_{max} cm^{-1}). Vanillin Schiff's bases (I) were prepared by a reported procedure[11].

2-Methoxy-4-(N-substituted arylidino)phenoxy acetic acid ethyl ester(II)

A mixture of appropriate vanillin Schiff's base (0.1 mole), chloroethyl acetate (0.1 mole) and potassium carbonate (0.12 mole) was refluxed in dry acetone for 24 h. The reaction mixture was filtered while hot. The filtrate was concentrated by distilling the excess solvent under reduced pressure. The solid mass that separated out on cooling was filtered, dried and crystallised from ethanol. These compounds (Table-1) were characterised by analysis, melting points and characteristic IR bands (cm^{-1}) at 1740–1720 (C=O, ester), 1620–1610 (C=C, aromatic), 1580–1570 (C=N, stretching) and 1460–1450 (C—N, stretching).

TABLE-1
ANALYTICAL DATA OF 2-METHOXY-4-(N-SUBSTITUTED ARYLIDINO)PHENOXY ACETIC ACID ETHYL ESTERS (IIa-e) AND HYDRAZIDES (IIIa-e)

Compd. No.	—R	m.p. (°C)	Yield (%)	Molecular Formula	% N	
					Found	Calcd.
IIa	—H	78	73	$C_{18}H_{19}NO_4$	4.20	4.47
IIb	—CH_3	90	78	$C_{19}H_{21}NO_4$	4.05	4.28
IIc*	—Cl	80	71	$C_{18}H_{18}ClNO_4$	3.82	4.02
IId	—Br	84	69	$C_{18}H_{18}BrNO_4$	3.25	3.57
IIe	—I	101	67	$C_{18}H_{18}INO_4$	2.85	3.19
IIIa	—H	150	64	$C_{16}H_{17}N_3O_3$	13.96	14.04
IIIb	—CH_3	153	66	$C_{17}H_{19}N_3O_3$	13.10	13.41
IIIc†	—Cl	193	63	$C_{16}H_{16}ClN_3O_3$	12.28	12.56
IIId	—Br	168	61	$C_{16}H_{16}BrN_3O_3$	10.83	11.11
IIIe	—I	121	58	$C_{16}H_{16}IN_3O_3$	9.53	9.88

*Lit (12) m.p., 70°C

†Lit (12) m.p., 198–99°C

2-Methoxy-4-(N-substituted arylidino)phenoxy acetic acid hydrazide (III)

A mixture of appropriate 2-methoxy-4-(N-substituted arylidino)phenoxy acetic acid ethyl ester (II) (0.01 mole) and hydrazine hydrate, 98% (0.012 mole) was refluxed in ethanol for 6 h. The excess of solvent was removed by distillation under reduced pressure. The solid product that separated out was filtered and crystallised from ethanol to yield the required compounds. These compounds (Table-1) were characterised by analysis, melting points and characteristic IR bands (cm^{-1}) at 3300–3280 (N—H), 1680–1660 (CONH), 1620–1600 (C=C, aromatic and C=N) and 1420–1400 (C—N, stretch)

N-Benzylidine derivatives of 2-methoxy-4-(N-substituted arylidino)phenoxy acetic acid hydrazides (IV)

2-Methoxy-4-(N-substituted arylidino)phenoxy acetic acid hydrazide (0.01 mole) and an appropriate aromatic aldehyde (0.01 mole) was refluxed in acetic acid for 2 h. The product separated on cooling was filtered, washed with water and crystallised from acetic acid. The compounds (Table-2) were characterised by analysis, melting points and characteristic IR bands (cm^{-1}) at 3320–3300 (>N—H), 1680–1660 (—CONH), 1620–1600 (>C=C, aromatic and >C=N, stretch) and 1440–1430 (—C—N, stretch).

TABLE-2
ANALYTICAL DATA OF N-BENZYLIDINE DERIVATIVES OF 2-METHOXY-4-(N-SUBSTITUTED ARYLIDINO)PHENOXY ACETIC ACID HYDRAZIDES (IVa–y)

Compd. No.	—R	—R′	m.p. (°C)	Yield (%)	Molecular formula	% Nitrogen	
						Found	Calcd.
IVa	—H	—H	215	53	$C_{23}H_{21}N_3O_3$	10.49	10.85
IVb	—H	—*p*-NO_2	>250	49	$C_{23}H_{20}N_4O_5$	13.41	12.96
IVc	—H	—*p*-OCH_3	150	60	$C_{24}H_{23}N_3O_4$	9.79	10.07
IVd	—H	—*p*-CH_3	158–60	62	$C_{24}H_{23}N_3O_3$	9.89	10.47
IVe	—H	—*o*-OH	106	47	$C_{23}H_{21}N_3O_4$	10.08	10.42
IVf	—CH_3	—H	90	51	$C_{24}H_{23}N_3O_3$	10.10	10.47
IVg	—CH_3	—*p*-NO_2	>250	50	$C_{24}H_{22}N_4O_5$	13.07	12.55
IVh	—CH_3	—*p*-OCH_3	174	54	$C_{25}H_{25}N_3O_4$	10.00	9.74
IVi	—CH_3	—*p*-CH_3	170	59	$C_{25}H_{25}N_3O_3$	10.43	10.12
IVj	—CH_3	—*o*-OH	210	45	$C_{24}H_{23}N_3O_4$	9.76	10.07
IVk	—Cl	—H	92	61	$C_{23}H_{20}ClN_3O_3$	10.21	9.96
IVl	—Cl	—*p*-NO_2	>250	63	$C_{23}H_{19}ClN_4O_5$	11.43	11.20
IVm	—Cl	—*p*-OCH_3	200	56	$C_{24}H_{22}ClN_3O_4$	9.76	9.32
IVn	—Cl	—*p*-CH_3	187	55	$C_{24}H_{22}ClN_3O_3$	9.32	9.62
IVo	—Cl	—*o*-OH	220	43	$C_{23}H_{20}ClN_3O_4$	9.28	9.60

Compd. No.	—R	—R′	m.p. (°C)	Yield (%)	Molecular formula	% Nitrogen	
						Found	Calcd.
IVp	—Br	—H	82	46	$C_{23}H_{20}BrN_3O_3$	9.43	9.01
IVq	—Br	—*p*-NO_2	235	57	$C_{23}H_{19}BrN_4O_5$	11.23	10.95
IVr	—Br	—*p*-OCH	180	52	$C_{24}H_{22}BrN_3O_4$	8.05	8.47
IVs	—Br	—*p*-CH_3	137	49	$C_{24}H_{22}BrN_3O_3$	9.13	8.75
IVt	—Br	—*o*-OH	200	46	$C_{23}H_{20}BrN_3O_4$	9.00	8.71
IVu	—I	—H	168	54	$C_{23}H_{20}IN_3O_3$	8.52	8.18
IVv	—I	—*p*-NO_2	>250	52	$C_{23}H_{19}IN_4O_5$	9.76	10.03
IVw	—I	—*p*-OCH_3	208	58	$C_{24}H_{22}IN_3O_4$	8.11	7.73
IVx	—I	—*p*-CH_3	205	54	$C_{24}H_{22}IN_3O_3$	8.39	7.96
IVy	—I	—*o*-OH	210	48	$C_{23}H_{20}IN_3O_4$	7.55	7.93

Screening for antifungal activity

All the compounds (II), (III) and (IV) were screened for their antifungal activity against *Alternaria alternata, Aspergillus flavus* and *Fusarium moniliforme* as the test fungi by paper-disc plate method[13] at concentration levels of 2 and 0.2% (w/v) in dimethylformamide. Standard PDA medium was used. Filter paper discs of diameter 12 mm were used and the diameter of zones of inhibition formed around each disc after incubating for a period of 48 h at 25–28°C were recorded. Results were compared with a reference fungicide thiram 75 W. Compounds numbered IIb, IIe, IIIb, IIIe, IVb, IVf, IVg, IVk, IVq, IVu and IVv exhibited moderate antifungal activities against all the test fungi.

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