SYNTHESIS AND BIOLOGICAL ACTIVITIES OF SOME 1,3,4-OXADIAZOLES AND BIS (1,3,4-OXADIAZOLES)

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SUMMARY: Oxidative cyclization of hydrazones (1) derived from aromatic aldehydes and aroylhydrazines with iodine and yellow mercuric oxide gave 2,5-diaryl-1,3,4-oxadiazoles (2). Condensative cyclization of the same hydrazones by heating with acetic anhydride or benzoyl chloride in the presence of pyridine gave 3-acetyl-2,5- diaryl-2,3-dihydro-1,3,4-oxidiazoles (3) or 3-benzoyl-2,5- diaryl-2,3-dihydro-1,3,4-oxadiazoles (4). Dehydrogenative cyclization of oxalic or adipic acids bis (aroylhydrazides) (5 and 6) gave bis (5-aryl-1,3,4-oxadiazol-2-yl) (7) or 1,4-bis (5-aryl-1,3,4-oxadiazol-2-yl) butane (8). Bis (5-aryl-1,3,4-oxadiazol-2-yl (7) were also prepared by the oxidative cyclization of glyoxal bis (aroylhydrazones) (9). Bis (3-acetyl-5-aryl-2,3-dihydro-1,3,4-oxadiazol-2-yl) and bis (3-benzoyl-5-aryl-2,3-dihydro-1,3,4-oxadiazol-2-yl) derivatives (10 and 11) were obtained by condensative cyclization of glyoxal bis (aroylhydrazones) (9) with acetic anhydride or benzoyl chloride. Nematocidal, insecticidal, and herbicidal activities of some of the prepared compounds are reported.

Key Words: Hydrazones, hydrazides, cyclization, 1,3,4-Oxadiazoles, biological tests.

INTRODUCTION

The synthesis of 1,3,4-oxadiazoles is of considerable interest due to their various biological activities. Reported among these activities were: nervous system depressing (9), analgesic (2,11), herbicidal (7), muscle relaxant (20), and tranquilizing (12) activities. We were determined, therefore, to carry out investigations (4,10,15-17) towards the synthesis of various 1,3,4-oxadiazole derivatives in order to exploit some of their activities. In the present investigation we report on the synthesis of new members of this applicably important type of compounds from aroylhydrazones and hydrazides using three different routes namely: oxidative-, dehydrative-, and condensative- cyclizations.

RESULTS AND DISCUSSION

Oxidative cyclization of 4-chlorobenzaldehyde 4-chlorobenzoylhydrazone (18) (1a) with iodine and yellow mercuric oxide in dry ether gave a product which only showed C=N absorption band at 1610 cm^{-1} and lacked the CONH and NH bands present in the spectrum of the parent hydrazone. The ^1H NMR spectrum of this product also lacked the hydrazono NH and azomethine (CH=N) proton signals characteristic of the original hydrazone. This oxidation product was assigned, therefore, the 2,5-bis (4-chlorophenyl)-1,3,4-oxidiazole structure 2a. Similarly, hydrazones 1b, 1d, 1g, 1n, and 1r, were oxidatively cyclized to the corresponding 1,3,4-oxadiazoles 2b, 2d, 2g, 2n and 2r respectively. It is worth mentioning that the obtained 2- (4-chlorophenyl)-5-phenyl- 1,3,4- oxadiazole (2g) was found to be identical with that previously (4) prepared by the oxidative cyclization of benzaldehyde 4-chlorobenzoylhydrazone (18) (1h).

Heating hydrazone 1a with acetic anhydride gave a product having the molecular formula $C_{16}H_{12}N_3C_2O_2$ that showed CON absorption at 1670 cm^{-1}. In conformity with previously reported (1,19) results on other systems, the structure of 3-acetyl-2,5-bis(4-chlorophenxl)- 2,3-dihydro-1,3,4-oxidiazole (3a) was inferred to this product.

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Table 1: Physical, elemantal analysis and spectral data of 2,5-diaryl-1,3,4-oxadiazoles (2).

Compd. No.	R^1	R^2	MP (°C)	Yield (%)	Molecular Formula	Analyses (%) Calc./Found			IR (Nujol) cm^{-1}
						C	H	N	C=N
2a	4-Cl	4-Cl	252	71	$C_{14}H_6N_2Cl_2O$	57.7 58.1	2.7 2.6	24.4 24.2	1610
2b	4-OMe	4-OMe	162	71	$C_{16}H_{14}N_2O_3$	68.1 67.9	5.0 5.3	9.9 9.4	1620
2d	4-OAc	4-OAc	220	71	$C_{15}H_{14}N_2O_5$	63.9 64.1	4.2 4.1	8.3 8.3	1615
2g	4-Cl	H	165	81	$C_{14}H_9N_2C_{10}$	65.5 66.0	3.5 3.8	10.9 10.9	1612
2n	H	3-Me	113	60	$C_{15}H_{12}N_2O$	76.2 75.7	5.1 5.1	11.9 11.9	1615
2r	2-OAc	4-OAc	229	81	$C_{15}H_{14}N_2O_5$	63.9 63.9	4.2 4.3	8.3 8.2	1615

^{1}H NMR ($CDCl_3$) of 2 a δ 7.3 - 8.3 (m, 8H, aromatic H)

Similar condensative cyclizations of the hydrazones 1d, 1f, 1i, and 1n by boiling with acetic anhydride also gave the corresponding 3-acetyl-2,5-diaryl-2,3-dihydro-1,3,4-oxadiazoles 3d, 3f, 3i and 3n respectively. Heating 4-hydroxybenzoylhydrazone (1c) or benzaldehyde 4-aminobenzoylhydrazone (1k) with acetic anhydride resulted in condensative cyclization and concurrent acetylation of the hydroxyl or amino groups to give the 2,5-bis(4-acetoxyphenyl)-3-acetyl-2,3-dihydro-1,3,4-oxadiazole (3d) and 2-(4-acetamidophenyl)-3-acetyl-2,3-dihydro-5- phenyl- 1,3,4-oxadiazole (3i) respectively.

Condensative cyclization of 1a by heating with benzoyl chloride in the presence of pyridine at 100°C gave 3-benzoyl-2,5-bis (4-chlorophenyl)-2,3-dihydro-1,3,4-oxadiazole (4a). Upon similar treatment, hydrazones 1b, 1c, 1f, 1g, 1h, 1m, and 1o also gave the corresponding 3-benzoyl-2,5-bis-aryl-2,3-dihydro-1,3,4-oxadiazole 4b, 4e, 4f, 4g, 4h, 4m, and 4q respectively; the two hydrazones 1c and 1o underwent cyclization and concomitant benzoylation to give 4e and 4q.

Condensation of oxalyl chloride or adipoyl chloride with two molar equivalents of aroylhydrazines in dry benzene afforded the corresponding oxalic acid bis (aroylhydrazides) (5) and adipic acid bis (aroylhydrazides) (6) respectively. The IR spectra of these bis-hydrazide showed the expected CONH and NH absorptions. Subjecting these bis-hydrazides to dehydrative cyclization by heating with phosphoryl chloride gave products having two molecules of water less than the corresponding bis-hydrazides. These proucts showed only C=N absorptions and lacked the CONH and NH absorptions of the parent hydrazides and were, accordingly, assigned the structures of bis (5-aryl-1,3,4-oxadiazol-2-yl) (7a-7e) and 1,4-bis (5-aryl-1,3,4-oxadiazol-2-yl) butane (8a-8j) respectively.

Alternatively, bis (5-aryl-1,3,4-oxadiazol-2-yl) derivatives (7b-7f) were also obtained by the oxidative cyclization of glyoxal bis (aroylhydrazones) (9b-9f) with iodine and yellow mercuric oxide.

Condensative cyclization of glyoxal bis (aroylhydrazones) (9) by heating with acetic anhydride gave the bis (3-acetyl-5-aryl-2,3-dihydro-1,3,4- oxadiazol-2-yl) 10 which showed C=N and CON absorptions at 1605-1640 and 1665-1720 cm^{-1} respectively.

Heating 9a-9j with benzoyl chloride in the presence of pyridine at 100°C gave the bis (3-benzoyl-5-aryl-2-3- dihydro-1,3,4-oxadiazol-2-yl) derivatives 11a-11j.

RESULTS OF BIOLOGICAL TESTS

Nematocidal activity

Compound 10d showed no nematocidal activity against root knot nematode (*Moloidogyne incognita*) hosted on cucumbers (*Cucumis sativus*) at the rate of 10 ppm in the growth pouch screening assay.

Insecticidal activity

Compounds 4b, 4f, 10c, 11e, and 11j were found to be inactive against the yellow fewer mosquito larvea (*Aedes aegypti*) hosted in water at the rate of 1000 ppm for 48 hours. Compound 10d also showed no insecticidal activity when applied at the rate of 1000 ppm for 48 hours to the following insect species/host plant systems: beet armyworm (*Spodoptera exigua*)/pinto bean (*Phaseolus vulgaris*); mexican bean beatle (*Epilachna variventis Muslant*)/pinto bean; pea aphid (*Acrythosiphon pisum Harris*)

Table 2: Physical, elemantal analysis and spectral data of 3-acetyl-2.5 -diaryl-2,3 -dihydro-1,3-oxadiazoles (3) and 3-benzoy 1-2,5 -diaryl -2,3-dihydro -1,3-oxadiazoles (4).

Compd. No.	R^1	R^2	MP (°C)	Yield (%)	Molecular yses Formula	Analyses (%)			IR (Nujol) cm^{-1}	
						C	H	N	CON	C=N
3a*	4-Cl	4-Cl	128	85	$C_{16}H_{12}N_2Cl_2O_2$	57.3 57.0	3.6 3.5	8.4 8.2	1670	1640
3d	4-OAc	4-OAc	210	80	$C_{20}H_{16}N_2O_6$	62.8 62.6	4.7 4.9	7.3 7.0	1670	1615
3f	4-NO_2	4-NO_2	186	77	$C_{16}H_{12}N_4O_6$	54.0 54.3	4.0 4.8	15.7 15.2	1680	1630
3i	H	4-Me	136	62	$C_{17}H_{16}N_2O_2$	72.8 72.8	5.8 6.3	10.0 9.8	1670	1620
3l	H	4-N-Ac	222	60	$C_{15}H_{17}N_3O_3$	66.9 66.8	5.3 7.5		1650	1608
3n	H	3-Me	220	62	$C_{17}H_{16}N_2O_2$	72.8 73.1	5.8 6.1		1670	1650
4a**	4-Cl	4-Cl	142	81	$C_{21}H_{14}N_4Cl_2O_2$	63.5 63.4	3.6 3.8	7.1 6.7	1660	1600
4b	4-OMe	4-OMe	144	69	$C_{23}H_{20}N_4O_2$	71.1 71.4	5.2 5.4	7.2 7.0	1638	1638
4e	4-OBz	4-OBz	215	63	$C_{35}H_{24}N_2O_6$	73.9 73.6	4.3 4.2	5.0 5.2	1638	1602
4f	4-NO_2	4-NO_2	194	83	$C_{21}H_{14}N_4O_6$	60.3 60.1	3.4 3.1	13.4 12.9	1640	1642
4g	4-Cl	H	134	57	$C_{21}H_{15}N_2Cl_2O$	69.5 70.1	4.2 4.3	7.7 7.9	1685	1610
4h	H	4-Cl	131	64	$C_{21}H_{15}N_2Cl_2O$	69.5 70.1	4.2 4.1	7.7 8.0	1641	1630
4m	H	3-Cl	148	30	$C_{21}H_{15}N_2Cl_2O$	69.5 69.2	4.2 4.5	9.8 9.8	1650	1600
4g	2-OBz	H	115	56	$C_{25}H_{20}N_2O_4$	75.0 74.8	4.5 4.8	6.3 6.7	1643	1618

*^{1}H NMR ($CDCl_3$): δ 8.1 - 7.0 (m, 8H, aromatic H), 6.80 ($_5$, 1H, oxadiazoline CH) and 2.40 ($_5$.3H, CH_3)
**^{1}H NMR ($CDCl_3$): δ 7.2 - 8.3 (m, 14H, 13 aromatic H+oxadiazoline CH)

/fava bean (*Vicia faba*); and two-spotted spider mite (*Tetranychus urticae*)/pinto bean.

Herbicidal activity

Compounds 4b, 4f, 10c, 11e, and 11j exhibited no herbicidal activity in the pre-emergence response and low activity (<10%) in the post-emergence response screening when applied to the following species: Soybean (*Glycine max*), Corrn (*Zeamays*), wheat (*Triticum aestivum*), morningglory (*Ipomea spp.*), velvetleaf (*Abutilon theophrasti*), barnyardgrass (*Echinochloa crus-gali*), and foxtail green (*Setaria veridis*).

MATERIALS AND METHODS

General Methods

Melting points were determined with a kofler block and are uncorrected. The infrared spectra (IR) were recorded for nujol mulls on SP-1100 spectrophotometer. Proton magnetic resonance (^{1}H NMR) spectra were carried out with a Varian T6o spectrometer. Follow up of the reactions and checking the homogeneity of the prepared compounds were made by performing thin-layer chromatography (tlc) on Sillica gel G (Merck) precoated plates (layer thickness 0.25 mm) used without pretreatment. All ratios of the solvent systems used for elution were volume-to-volume (v/v), the distance of the solvent travel was 5 cm, and the spots were detected by exposure to iodine vapour for a few minutes. Solvent evaporations were performed in a rotary evaporator under diminished pressure with an outside bath temperature kept blow 50°C. Elemental microanalyses were preformed in the Microanalysis Laboratory, Department of Chemistry, Faculty of Science, Alexandria University using Perkin-Elmer Model PE-240 analyzer or in the Microanalysis Unit, Faculty of Science, Cairo University.

The following known hydrazones were prepared according to methods described in literature: 4-chlorobenzaldehyde 4-chlorobenzoylhydrazone (1a) (18), 4-methoxybenzaldehyde 4-methoxy-benzoylhydrozne (1b) (8) 4-hydroxybenzaldehyde

4-hydroxybenzoylhydrazone (1c) (3), 4-nitrobenzaldehyde 4-nitrobenzoylhydrazone (1f) (6), 4-chlorobenzaldehyde benzoylhydrazone (1g) (18), benzaldehyde 4-chlorobenzoylhydrazone (1h) (18) benzaldehyde 3-chlorobenozylhydrazone (1m) (14), benzaldehyde 4-methyl- benzoylhydrazone (1i) (13), benzaldehyde 3-methylbenzoylhydrazone (1n) (13), and salicyalaldehyde benzoylhydrazne (10) (5).

4-Acetoxybenzaldehyde 4-acetoxybenzoylhydrazone

A solution of 4-hydroxybenzaldehyde 4-hydroxybenzoylhydrazone (3) (1c. 0.004 mole) in pyridine (5 ml) was stirred with acetic anhydride (10 ml) at room temperature for 24 hours. The mixture was poured onto crushed ice and the product which separated was filtered, washed with water, dried, and crystallized from ethanol to give 0.8 g (60%) of 1d, m.p. 230°; IR: 3280, 3240

Table 3: Physical, elemantal analysis and spectral data of oxalyl bis (Aroylhydrazides) (5), adipoly bis (Aroylhydrazides) (6) and glyoxal bis (Aroylhydrazones) (9).

Compd. No.	R	MP (°C)	Yield (%)	Molecular Formula	Analyses (%) Calc./Found			IR (Nujol) cm^{-1}		
					C	H	N	NH	CONH	C=N
5a	H	278	52	$C_{16}H_{14}N_4O_4$	58.8 59.3	4.3 4.2	17.1 17.0	3365	1675	
5b	4-Me	283	57	$C_{18}H_{18}N_4O_4$	61.0 60.9	5.1 5.1	15.8 15.6	3230	1665	
5c	3-Me	296	46	$C_{18}H_{18}N_4O_6$	61.0 60.5	5.1 5.4	15.8 15.7	3450	1680	
5d	4-OMe	291	52	$C_{18}H_{18}N_4O_6$	55.9 55.9	4.7 4.4	14.5 15.0	3380	1695	
5e	4-Cl	3.8	52	$C_{18}H_{18}N_4Cl_2O_4$	48.7 48.8	3.0 3.3	14.2 14.0	3190	1630	
6a	H	240	58	$C_{20}H_{22}N_4O_5$	62.8 63.2	5.8 5.4	14.7 14.9	3365	1670	
6b	4-Me	283	59	$C_{22}H_{26}N_4O_4$	64.4 64.1	6.4 6.1	13.6 13.6	3200	1660	
6c	3-Me	295	45	$C_{22}H_{26}N_4O_6$	64.4 64.1	6.4 6.1	13.6 14.1	3225	1680	
6d	4-OMe	278	50	$C_{22}H_{26}N_4O_6$	59.7 60.2	5.9 5.8	12.6 12.6	3270	1670	
6e	4-Cl	313	72	$C_{20}H_{20}N_4Cl_2O_4$	53.2 53.2	4.5 4.4	12.4 12.2	3250	1670	
6f	3-Cl	268	52	$C_{20}H_{20}Cl_2O_4$	53.2 53.4	4.5 4.7	12.4 12.8	3240	1680	
6g	2-Cl	301	48	$C_{20}H_{20}N_4Cl_2O_4$	53.2 53.0	4.5 4.6	12.4 12.4	3250	1675	
6h	4-Br	315	59	$C_{20}H_{20}N_4Br_2O_4$	44.5 44.6	3.7 4.0	10.4 10.5	3250	1665	
6i	3-Br	280	52	$C_{20}H_{20}N_4Br_2O_4$	44.5 44.8	3.7 3.8	10.4 10.5	3220	1675	
6j	4-NO_2	301	46	$C_{20}H_{20}N_6O_6$	50.8 51.2	4.3 4.0	17.9 17.4	3240	1625	
9b	4-Me	350	90	$C_{15}H_{15}N_4O_2$	67.1 67.3	5.6 5.1		3450	1660	1610
9c	3-Me	300	82	$C_{15}H_{15}N_4O_2$	67.1 67.3	5.6 5.4		3450	1660	1615
9d	4-OMe	350	83	$C_{18}H_{18}N_4O_4$	61.0 60.5	5.1 5.3	15.8 15.3	3450	1650	1650
9e	4-Cl	300	86	$C_{16}H_{12}N_2Cl_2O_2$	52.9 53.0	3.3 3.1	15.4 15.6	3450	1670	1600
9f	3-Cl	350	74	$C_{16}H_{12}N_4Cl_2O_2$	52.9 52.8	3.3 3.7	15.4 14.9	3450	1655	
9g	2-Cl	300	85	$C_{16}H_1N_4Cl_2O_2$	52.9 52.8	3.3 3.8		3450	1665	
9i	3-Br	300	79	$C_{16}H_{12}N_4Br_2O_2$	42.5 42.4	2.7 3.2	11.7 11.3	3340	1685	
9j	4-NO_2	300	85	$C_{16}H_{12}N_6O_6$	50.0 50.0	3.2 3.6		3400	1675	1625

(NH), 1725, 1712 (CONH), 1645 and 1618 cm^{-1} (C=N). Anal. ($C_{18}H_{16}N_2O_5$):

	C	H
Calc	63.5	4.7
Found	64.0	4.8

2-Acetoxybenzaldehyde 4-acetoxybenzoylhydrazone (1r)

The title compound was prepared from salicylaldehyde 4-hydroxybenzoylhydrazone (5) (10) as just described for the preparation of 1d.

Yield: 53%, m.p. 152°; IR: 3200 (NH), 1775 (OAc), 1670 (CONH) and 1612 cm^{-1} (C=N). Anal. ($C_{18}H_{16}N_2O_5$):

	C	H	N
Calc	63.5	4.7	8.2
Found	63.3	4.7	8.1

2,5-Diaryl-1,3,4-oxadiazoles (2)

A suspension of the particular aromatic aldehyde aroylhydrazone (1, 0.004 mole) was successively treated with yellow mercuric oxide (2 g), magnesium oxide (0.2 g) and iodine (1 g)

Table 4: Physical, elemantal analysis and spectral data of bis (5-Aryl-1,3-4-Oxadioazol-2-yl) (7) and 1,4-bis (5-Aryl-1,3,4-Oxadiazol-2-yl) butanes (8).

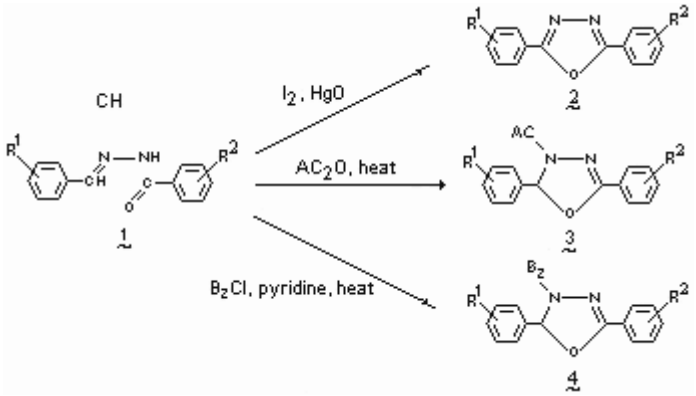
Compd. No.	R	MP (°C)	Method of Cyclization	Yield (%)	Molecular Formula	Analyses (%) Calc./Found			IR (Nujol) cm^{-1}
						C	H	N	C=N
7a	H	286	A	79	$C_{16}H_{10}N_4O_2$	66.2 66.2	3.5 3.5	19.3 19.1	1610
7b	4-Me	265	A B	77 51	$C_{18}H_{14}N_4O_2$	67.9 67.9	4.4 4.1	17.6 17.5	1622
7c	3-Me	296	A	67	$C_{18}H_{14}N_4O_2$	67.9 67.3	4.4 4.0	17.6 17.8	1600
7d	4-OMe	290	A B	78 41	$C_{18}H_{14}N_4O_4$	61.7 61.7	4.0 4.4	16.0 15.7	1618
7e*	4-Cl	224	A B	88 41	$C_{16}H_8N_4Cl_2O_2$	53.5 53.6	2.2 2.2	15.6 15.7	1610
7f	3-Cl	190	B	70	$C_{30}H_{20}N_4Cl_2O_4$	63.1 63.4	3.5 4.0	9.8 10.0	1610
8a	H	144	A	78	$C_{20}H_8N_4O_2$	69.3 69.5	5.2 5.2	16.2 16.3	1615
8b	4-Me	154	A	77	$C_{22}H_{22}N_4O_2$	70.5 70.1	5.9 6.0	15.0 14.5	1610
8c	3-Me	208	A	44	$C_{22}H_{22}N_4O_2$	70.5 70.0	5.9 6.1	15.0 14.7	1605
8d**	4-OMe	278	A	50	$C_{22}H_{22}N_4O_2$	70.5 70.1	5.9 6.0	15.0 14.5	1610
8e***	4-Cl	199	A	76	$C_{20}H_{16}N_4Cl_2O_2$	58.0 57.7	3.9 4.0	13.5 13.2	1615
8f	3-Cl	139	A	65	$C_{20}H_{16}N_4Cl_2O_2$	58.0 58.1	3.9 3.9	13.3 13.5	1605
8g	2-Cl	120	A	43	$C_{20}H_{16}N_4Cl_2O_2$	58.0 58.0	3.9 3.5	13.3 13.5	1610
8h	4-Br	315	A	65	$C_{20}H_{16}N_4Br_2O_2$	47.6 48.1	3.2 3.0	11.1 10.6	1610
8i	3-Br	142	A	55	$C_{20}H_{16}N_4Br_2O_2$	47.6 47.6	3.2 3.5	11.1 10.6	1610
8j	4-NO_2	235	A	56	$C_{20}H_{16}N_6O_6$	55.1 55.2	3.6 3.6	19.2 18.9	1613

* ^{1}HNMR ($CDCl_3$): δ 7.25 (5, 8H, aromatic H)

** ^{1}HNMR ($CDCl_3$): δ 7.90 - 6.86 (m. 8H, aromatic H) and 3.8 (5, 6H2CH_3)

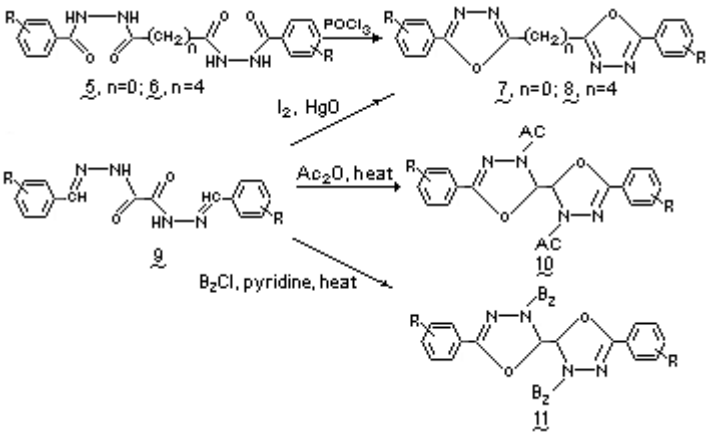
*** ^{1}HNMR ($CDCl_3$): δ 2.96 and 1.96 (2m, 4H, CH_2 each)

Scheme 1



a; $R^1 = R^2$ = 4-Cl
b; $R^1 = R^2$ = 4-OMe
c; $R^1 = R^2$ = 4-OH
d; $R^1 = R^2$ = 4-OAc
e; $R^1 = R^2$= 4-OBz
f; $R^1 = R^2$= 4-NO_2
g; R^1 = 4-Cl, R^2= H
h; R^1 = H, R^2= 4-Cl
i; R^1 = H, R^2 = 4-Me
k; R^1 = H, R^2 = 4-NH^2
l; R^1 = H, R^2 = 4-NHAc
m; R^1 = H, R^2 = 3-Cl
n; R^1 = H, R^2= 3-Me
o; R^1 = 2-OH, R^2= H
p; R^1 = 2-OAc; R^2= H
q; R^1 = 2-Bz; R^2= H
r; R^1 = 2-OAc; R^2= 4-OAc

Scheme 2



a, R = H
b, R = 4-Me
c, R = 3-Me
d, R = 4-OMe
e, R = 4-Cl
f, R = 3-Cl
g, R = 2-Cl
h, R = 4-Br
i, R = 3-Br
j, R = 4-NO_2

and the mixture was kept at ambient temperature for 24 hours while stirring. The ethereal solution was filtered and the inorganic residue was washed with chloroform (4x50 ml). The combined ethereal and chloroform solutions were washed with saturated potassium iodide and sodium thiosulphate solutions and water and dried (Na_2SO_4). Evaporation of the solvents yielded a residue which crystallized from ethanol to give the title compounds (Table 1).

3-Acetyl-2,5-diaryl-2,3-dihydro-1,3,4-oxadiazoles (3)

A mixture of the particular aldehyde aroylhydrazone (1, 0.004 mole) and acetic anhydride (50 ml) was heated under reflux for 4 hours. The mixture was evaporated to dryness and the residue was crystallized from ethanol to give the title compounds (Table 2).

3-Benzol-2,5-diaryl-2,3-dihydro-1,3,4-oxadiazoles (4)

A solution of the particular hydrazone (1, 0.004 mole) in pyridine (6 ml) was treated with benzoyl chloride (3 ml) and the mixture was heated on a water-bath for 6 hours. The reaction mixture was poured onto crushed ice and the product which separated was filtered, washed with water, dried, and crystallized from ethanol (Table 2).

Oxalyl bis (aroylhydrazides) (5) and adipoyl bis (aroylhydrazides) (6)

A solution of the appropriate aroylhydrazine (0.01 mole) in dry benzene (200 ml) was treated with oxalyl chloride (0.008 mole) and the mixture was left at ambient temperature for 4 hours. The product which separated was filtered, washed with hot ethanol and dried to give the title compounds (Table 3).

Glyoxal bis (aroylhydrazones) (9)

To a suspension of glyoxal bis (sodium hydrogen sulfite (0.03 mole) in water (100 ml), cation exchange resin (Dowex 50, H^+ form) was added and the mixture was stirred at ambient temperature for 10 minutes. The resin was filtered through a fritted-glass funnel and the filtrate was treated with a solution of the appropriate aroylhydazine (0.03 mole) in methanol (100 ml). The mixture was heated on a water-bath for 10 minutes and the product, which separated after attaining room temperature, was filtered and washed several times with filtered methanol to give the highly insoluble title compounds (Table 3).

Bis (5-aryl- 1,3,4-oxadiazol-2-yl) (7) and 1,4-bis (5-aryl-1,3,4-oxadiazol-2-yl) butane (8)

Method (A)

The particular oxalyl bis (aroylhydrazine) (5, 0.003 mole) or adipoyl bis (aroylhydrazine) (6, 0.002 mole) was treated with phosphoryl chloride (15 ml) and heated under reflux for an hour. After attaining ambient temperature, the mixture was poured onto a cold saturated solution of sodium hydrogen carbonate

Table 5: Physical, elemantal analysis and spectral data of bis (3-Acetyl-5-aryl-2,3-Dihydro-1,3,4-Oxadiazol-2-yl) (10) and bis (3-Benzoyl-5-aryl-2,3-Dihydro-1,3,4-Oxadiazol-2-yl) (11).

Compd. No.	R	MP (°C)	Yield (%)	Molecular Formula	Analyses (%) Calc./Found			IR (Nujol) cm^{-1}	
					C	H	N	CON	C=N
10a	H	242	62	$C_{20}H_{15}N_4O_4$	63.5 63.3	4.8 5.1	14.8 14.8	1760	1630
10b	4-Me	223	60	$C_{22}H_{22}N_4O_4$	65.0 65.0	5.5 5.5	13.7 13.9	1700	1680
10d	4-OMe	270	60	$C_{22}H_{24}N_4O_6$	60.3 59.8	5.1 4.7	12.8 13.2	1665	1640
10e	4-Cl	245	53	$C_{20}H_{16}Cl_2O_4$	53.7 53.7	3.6 4.2		1720	1645
10g	2-Cl	210	60	$C_{20}H_{16}N_4Cl_2O_4$	53.7 53.8	3.6 3.9	12.5 12.7	1670	1640
10h	4-Br	232	68	$C_{20}H_{16}N_4Br_2O_4$	44.8 45.3	3.0 3.4	10.4 10.2	1670	1635
10i	3-Br	230	76	$C_{20}H_{16}N_4Br_2O_4$	44.8 44.7	3.0 2.8	10.4 10.3	1675	1640
10j	4-NO_2	215	66	$C_{20}H_{16}N_6O_6$	51.3 51.3	3.4 3.6	17.9 18.2	1680	1640
11a	H	213	71	$C_{30}H_{22}N_4O_4$	71.7 72.2	4.4 4.7	11.1 11.0	1680	1640
11b	4-Me	223	67	$C_{32}H_{26}N_4O_4$	72.4 72.6	4.9 4.7	10.6 10.2	1660	1638
11c	3-Me	175	73	$C_{32}H_{26}N_4O_4$	72.4 72.4	4.9 4.8	10.6 10.1	1630	1605
11d	4-OMe	240	60	$C_{32}H_{26}N_4O_6$	68.3 67.9	4.7 4.5	9.9 9.8	1690	1650
11e	3-Cl	236	60	$C_{30}H_{20}N_4Cl_2O_4$	63.1 63.1	3.5 3.5	9.8 9.8		1640
11f	3-Cl	190	70	$C_{30}H_{20}N_4Cl_2O_4$	63.1 63.4	3.5 4.0	9.8 10.0	1672	1610
11h	4-Br	265	75	$C_{30}H_{20}N_4Br_2O_4$	54.6 54.4	3.1 3.5	8.5 9.0	1650	1635
11i	3-Br	170	68	$C_{30}H_{20}N_4Br_2O_4$	54.8 54.4	3.1 3.0	8.5 8.3	1690	1710
11j	4-NO_2	250	71	$C_{30}H_{20}N_6O_5$	60.8 61.2	3.4 3.9	11.2 14.3	1640	1705

and the product which separated was filtered off, washed with water, dried and crystallized from ethanol to give the corresponding title compounds (Table 4).

Method (B)

Glyoxal bis (aroylhydrazones) (9) were subjected to oxidative cyclization with iodine and yellow mercuric oxide as described for the preparation of 2,5-diaryl-1,3,4-oxadiazol (2).The products were crystallized from ethanol (Table 4).

Bis (3-acetyl-5-aryl-2,3-dihydro- 1,3,4-oxadiazol-2-yl) (10)

The title compounds were prepared by heating glyoxal bis (aroylhydrazones) (10) with acetic anhydride (10) as described for the preparation of 3-acetyl-2,5-diaryl-2,3-dihydro-1,3,4-oxadiazoles (3). The products were crystallized from ethanol (Table 5).

Bis (3-benzoyl-5-aryl-2,3-dihydro-1,3,4-oxadizol-2-yl) (11)

The title compounds were prepared by heating glyoxal bis (aroylhydrazones) (9) with benzoyl chloride and pyridine as described for the preparation of 3-benzoyl-2,5-diaryl-2,3-dihydro-1,3,4- oxadiazoles (4). The products were crystallized from ethanol (Table 5).

REFERENCES

1. Abdel Rahman MM, El Ashry EH, Abdallah AA, Rashed N : C-(Polyacetoxy) alkyloxadiazolines and related compounds. Carbonhydr Res, 73:103-111, 1979.

2. Angilini I, Angilini L, Sparacc F : 2-Phenyl-5-chloroalkyl-1,3,4-oxadiazoles, British Patent, 1:161, 801, 1969; Chem Abstr 71:112936, 1969.

3. Buu-Hoi NG ph, Xnong NGD, Nam NGH, Binon F, Rayer R : Tuberculostic hydrazides and their derivatives. J Chem Soc 1358-1364, 1953.

4. El Khadem H, Shaban MAE, Nassr MAM : Saccharide oxadiazoles, Carbohydr Res, 13:470-471, 1970.

5. Grammaticakis P : Spectral study of the nitrogen derivatives of some aromatic aldehydes and ketones. VII. Hydrazones and acyhdrazones. Bull Soc Chim France 690-698, 1950; Chem Abstr 45, 4646, 1951.

6. Grammaticakis P : Contribution to the study of absorption in the ultraviolet and visible region of aryl and aroylhydrazones. IV. Nitrobenzoylhydrazones, Bull Soc Chim France 659-669, 1955, Chem Abstr 50, 4830, 1956.

7. Kennedy DA, Summers LA : Chemical constitution and activity of Herbicides. Part XIV. Reduction potential and herbicidal activity of 4,4-(1,3,4-thiadiazole-2,5-diyl)-and 4,4-(1,3,4-oxadiazole-2,5-diyl) bis (1-methylpyridinium) diiodides, J Heterocycl Chem 409-410, 1981.

8. Khisamutinova F, Goryaev MI : Antitubercular compounds. VII. Synthesis starting with anisic acid and anisaldehyde, Akad Nauk Kazhk SSR 4:122-129, 1958. Chem Abstr 54:380, 1960.

9. Maillard J, Vincent M, Morin R, Benard M : Hypnotic and sedative drug, 2-(O-hydoxyphenyl) -1,3,4-oxadiazole. French Patent M 379: Chem Abstr: 57, 15251, 1962.

10. Nassr MAM, El-Badry SM, Shaban MAE : Reactions of aroylhydrazones. IV: Synthesis of nitrogen heterocycles from opianic acid hydrazones. J Chinese Chem Soc 32:65-73, 1985.

11. Najer H, Giudicelli R, Moral C, Menin M : Synthesis of some 5-aryl-2-dimethylamino-1,3,4-oxadiazoles with antiinflammatory action. Bull Soc Chem France 153-159, 1966.

12. Piala JJ, Yale HL : 2-Amino-5-aryl 1,3,4-oxadiazoles, US Patent: 3,141, 022, 1964. Chem Abstr: 61, 8317, 1964.

13. Sah PT, Tseu C : Hydrazines. V. m-Tolylyhdrazines as a reagent for the identification of aldehydes and ketones. Science Repts Natl 403-407, 1936, Chem Abstr 30:7104, 1936.

14. Sah PT, Wu CS : m Chlorobenzoyldrazides as a reagent for the identification of aldehydes and ketones. Science Repts Natl 443-449, 1936; Chem Abstr 30:0148, 1936.

15. Shaban MAE, Nassr MAM : Saccharide oxadiazoles. Carbodhydr Res, 36:C12-C13, 1974.

16. Shaban MAE, El Ashry EH, Nassr MAM, Reinhold VN : Saccharide oxadiazoles, Carbohydr Res, 42:C1-C3, 1975.

17. Shaban MAE, Nassr MAM : Saccharide 1,3,4-oxadiazoles, Org Prp Proced Int 8:107-112, 1976.

18. Shih C, Sah PT : p. chlorobenzoylhdrazide as a regent for the identification of aldehydes and ketones, Science Repts Natl 2:353-357, 1934, Chem Abstr 29:466, 1935.

19. Somogy L : 1,3,4-Oxadiazolines via acetylation of D-galactose acylhydrazones. Carbohydr Res 54:C14-C16, 1977.

20. Yale HI, Losee K : 2-Amino-5-substituted 1,3,4-oxadiazoles and 5-imino-substituted Δ^{2}- 1,3,4-oxadiazolines. A group of novel muscle relaxants. J Med Chem 9:478-483, 1966.

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