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Synthesis of New Series of 1,8-Bis-(4-Aryl Amino Methyl 1,3,4-Oxadiazolyl-5-Thion-2-yl) Octanes, 1,8-Bis-(5-Thio Acetic/ Formic Acid Hydrazide/Acetic Acid 1,3,4-Oxadiazol-2-yl) Octanes†

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Sebacic acid dihydrazide on refluxing with alcoholic potassium hydroxide and carbon disulphide afforded 1,8-bis-(1,3,4-oxadiazolyl 5-thione-2-yl) octane(II). Compound (II) on reacting with ethylchloroformate and ethylchloroacetate yielded the liquid esters (III and IV). The esters thus obtained on reacting with hydrazine hydrate afforded 1,8-bis-(5-thioformic/acetic acid hydrazide 1,3,4-oxadiazol-2-yl) octanes (V and VI). The compound (II) on reacting with various aromatic amines with formaldehyde yielded 1,8-bis-(4-aryl amino methyl 1,3,4-oxadiazol-5-thione-2-yl) octanes (VII a–l). The compound (II) on further reacting with chloroacetic acid afforded 1,8-bis-(5-thioacetic acid 1,3,4-oxadiazol-2-yl) octane (VIII).

INTRODUCTION

Compounds containing bis-triazole, bis-oxadiazole ring systems are known to possess fungicidal[1], pesticidal[2], insecticidal[3], bactericidal[4] and antiinflammatory[5] activities. Some of bis-oxadiazoles and bis-triazoles synthesized recently have been reported to display fungicidal activities[6]. 1,8-Bis-N-amino triazoles and 1,8-bis-oxadiazoles synthesised by our research group have shown anti-HIV, antifertility and anticancer, particularly prostate cancer[7] activities. Bis-1,3,4-oxadiazoline-2-thiones are associated with broad spectrum of biological activities such as analgesic, muscle relaxant and tranquillising properties[8–10].

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded in KBr pellets on Hi-tachi 230 infrared spectrophotometer. ^{1}H NMR spectra were recorded on a Varian 100 MHz spectrophotometer using TMS as an internal standard (chemical shifts are expressed in δ ppm)

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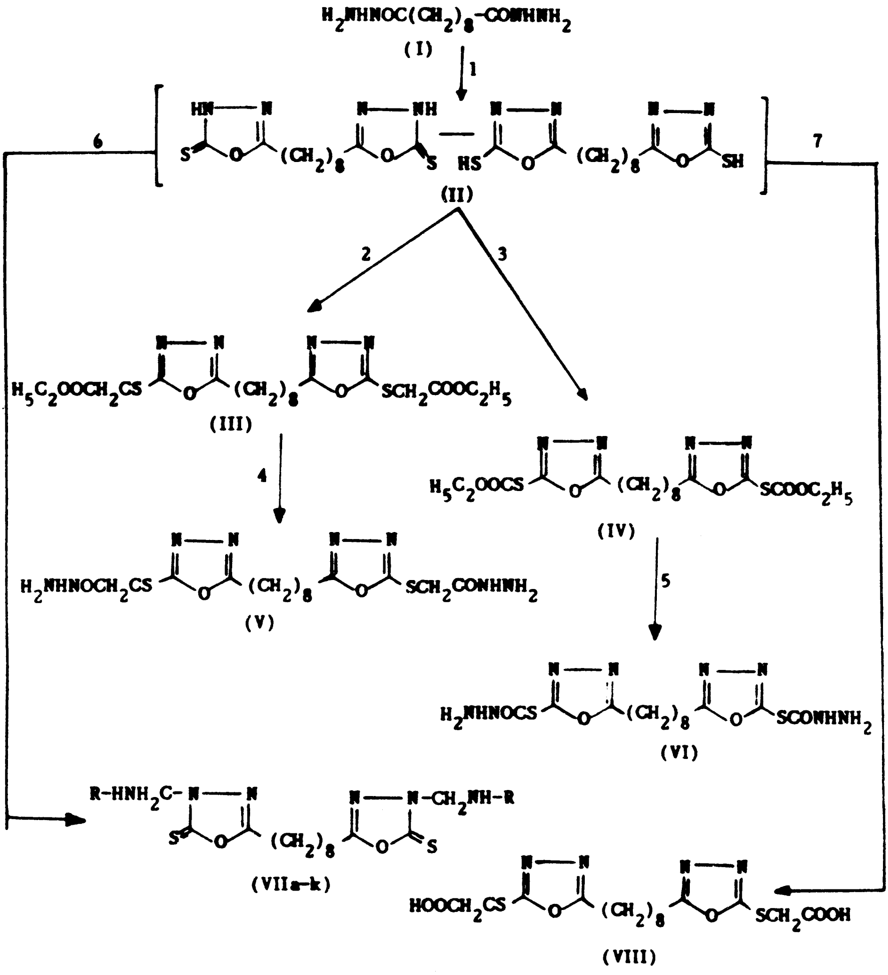
Scheme



1. $KOH(alc)/CS_2$; 2. $ClCH_2COOC_2H_5$; 3. $ClCOOC_2H_5$; 4,5. NH_2NH_2 (99%)
6. $R-NH_2/HCHO$ (40%)/alc; 7. $ClCH_2COOH/NaOH$ (8%)

Where	R	Where	R
VIIa	C_6H_5	VIIg	$4-Cl-C_6H_4$
VIIb	$2-CH_3-C_6H_4$	VIIh	$2-OCH_3-C_6H_4$
VIIc	$3-CH_3-C_6H_4$	VIIi	$4-OCH_3-C_6H_4$
VIId	$4-CH_3-C_6H_4$	VIIj	-Naphthalene
VIIe	$2-Cl-C_6H_4$	VIIk	-Naphthalene
VIIf	$3-Cl-C_6H_4$		

Preparation of sebacic acid dihydrazide (I)[11]

A mixture of diethyl sebacate (0.1 mol) and hydrazine hydrate (99%) (0.2 mol) in dry alcohol (50 mL) was refluxed on water bath for about 5 h. Sebacic acid dihydrazide was separated as a white crystalline solid; the reaction mixture was cooled to room temperature and the separated solid was filtered, dried and crystallised from aqueous ethanol.

Preparation of 1,8-bis-(5-mercapto 1,3,4-oxadiazol-2-yl) octane (II)

A mixture of sebacic acid dihydrazide (0.1 mol) and potassium hydroxide (0.3 mol) in absolute ethanol (50 mL) was refluxed on water bath for about 1 h and carbon disulphide (0.3 mol) was slowly added to it. The reaction mixture was refluxed further for 8–10 h. Excess of ethanol was removed and the residual mass was poured onto crushed ice and acidified with dilute acetic acid. The white solid thus separated was filtered, washed with cold water, dried and crystallised from ethanol. The compound thus obtained is listed in the Table.

IR: For compound (II): 3300–3200 cm^{-1} ν(NH), 2950–2900 cm^{-1} $\nu(CH_2)$, 2565 cm^{-1} ν(SH), 1610 cm^{-1} ν(C═N), 1240 cm^{-1} ν(C═S) and 1180–1140 cm^{-1} ν(C—O—C) ^{1}H NMR. For compound (II): 1.5–2.5 δ (16H, CH_2), 2.5 δ (1H, SH) and 7.5 δ (1H, NH).

Preparation of 1,8-bis (5-thioformic/acetic acid hydrazide 1,3,4-oxadiazol-2-yl) octane (V and VI)

1,8-Bis-(5-mercapto 1,3,4-oxadiazol-2-yl) octane (0.001 mol) was refluxed with ethyl chloroformate/ethylchloroacetate (0.003 mol) in dry acetone (25 mL) and anhydrous potassium carbonate (0.003 mol) for about 28 h. The excess of acetone was distilled off. The reaction mixture was poured onto crushed ice. The oil was separated which was further extracted with ether and dried over anhydrous calcium chloride. The ether was evaporated to get liquid esters (III and IV), as the esters were moisture sensitive, hence they were used further for the preparation of hydrazide. The compound (III and IV) (0.001 mol) was refluxed with hydrazine hydrate (0.003 mol) in absolute alcohol (25 mL) for 8–10 h. The alcohol was removed under reduced pressure, the separated solid was filtered, washed with cold water, dried and crystallised from aqueous ethanol. All the compounds obtained were listed in the Table.

IR: For compound (VI): 3250–3300 cm^{-1} $\nu(NH, NH_2)$, 2950–2600 cm^{-1} $\nu(CH_2)$, 1750 cm^{-1} ν(C═O), 1580 cm^{-1} ν(C═N) and 1180–1140 cm^{-1} ν(C—O—C).

^{1}H NMR: For compound (VI): 1.5–2.58 (16H, CH_2), 8.5 δ (NH) and 8.2 δ (NH_2).

Preparationof 1,8-bis (4-aryl amino methyl 1,3,4-oxadiazolyl-5-thione-2-yl) octane (VII a–k)

A mixture of 1,8-bis (5-mercapto 1,3,4-oxadiazol-2-yl) octane(II) (0.001 mol), formaldehyde (40%, 2 mL) and substituted primary amines (0.002 mol) in absolute ethanol (20 mL) was stirred for about 2 h and left overnight. The solid mass thus separated was collected by filtration, washed with cold ethanol, dried and crystallised from ethanol. All the compounds thus synthesised were listed in the Table.

TABLE
CHARACTERISATION DATA OF THE COMPOUNDS PREPARED

Comp.	Substituents	Yield (%)	m.p. (°C)	Mol. formula	Analysis: found (Calcd.) %		
					C	H	N
II	—	78	92	$C_{12}H_{18}N_4O_2S_2$	45.80 (45.85)	5.74 (5.73)	17.88 (17.83)
III	—	72	—	$C_{20}H_{30}N_4O_6S_2$	49.40 (49.38)	6.18 (6.17)	11.55 (11.52)
IV	—	82	—	$C_{18}H_{26}N_4O_6S_2$	47.20 (47.16)	5.68 (5.67)	12.25 (12.22)
V	—	76	140	$C_{16}H_{26}N_8O_4S_2$	41.95 (41.92)	5.62 (5.67)	24.46 (24.45)
VI	—	72	160	$C_{14}H_{22}N_8O_4S_2$	39.10 (39.06)	5.20 (5.11)	26.08 (26.04)
VIIa	C_6H_5	84	150–152	$C_{26}H_{32}N_6O_2S_2$	59.55 (59.54)	6.19 (6.10)	16.08 (16.03)
VIIb	2-CH_3—C_6H_4	79	110–112	$C_{28}H_{36}N_6O_2S_2$	60.90 (60.86)	6.55 (6.52)	15.25 (15.21)
VIIc	3-CH_3—C_6H_4	68	138	$C_{28}H_{38}N_6O_2S_2$	60.91 (60.86)	6.54 (6.52)	15.28 (15.21)
VIId	4-CH_3—C_6H_4	75	152	$C_{28}H_{36}N_6O_2S_2$	60.80 (60.86)	6.56 (6.52)	15.22 (15.21)
VIIe	2-Cl—C_6H_4	78	130–140	$C_{26}H_{30}N_6O_2S_2Cl_2$	52.65 (52.61)	5.09 (5.05)	14.20 (14.16)
VIIf	3-Cl—C_6H_4	84	158–160	$C_{26}H_{30}N_6O_2S_2Cl_2$	52.63 (52.61)	5.08 (5.05)	14.14 (14.16)
VIIg	4-Cl—C_6H_4	86	133–135	$C_{26}H_{30}N_6O_2S_2Cl_2$	52.64 (52.61)	5.07 (5.05)	14.18 (14.16)
VIIh	2-OCH_3—C_6H_4	70	142–144	$C_{28}H_{36}N_6O_4S_2$	57.55 (57.53)	6.19 (6.16)	14.40 (14.38)
VIIi	4-OCH_3—C_6H_4	71	135	$C_{28}H_{36}N_6O_4S_2$	57.54 (57.53)	6.20 (6.16)	14.29 (14.38)
VIIj	α-Naphthalene	68	95	$C_{34}H_{36}N_6O_2S_2$	65.40 (65.38)	5.79 (5.76)	13.50 (13.46)
VIIk	β-Naphthalene	72	85	$C_{34}H_{36}N_6O_2S_2$	65.41 (65.38)	5.79 (5.76)	13.40 (13.46)
VIII	4-Br—C_6H_4	84	145	$C_{26}H_{30}N_6O_2S_2Br_2$	45.75 (45.74)	4.40 (4.39)	12.32 (12.31)
VIII	—	81	320	$C_{16}H_{22}N_4O_6S_2$	44.64 (44.65)	5.20 (5.11)	13.05 (13.02)

IR: For compound (VIIg): 3375 cm^{-1} ν(NH), 2950–2900 cm^{-1} ν(CH_2), 1590 cm^{-1} ν(C=N), 1250 cm^{-1} ν(C=S) and 1180–1140 cm^{-1} ν(C—O—C).

^1H NMR: For compound (VIIg): 1.5–2.5 δ (16H, CH_2), 4.8 δ (2H, CH_2), 5.1 δ (NH) and 6.5–8.2 δ aromatic proteins.

Preparation of 1,8-bis-(5-thioacetic acid 1,3,4-oxadiazol-2-yl) octane (VIII)

A mixture of 1,8-bis-(5-mercapto 1,3,4-oxadiazol-2-yl) octane (II) (0.001 mol), sodium hydroxide (8%, 10 mL) and monochloroacetic acid (0.002 mol) was refluxed for 6 h. The reaction mixture was poured into cold water, acidified with dilute acetic acid. The precipitate thus obtained was filtered, washed with cold water, dried and crystallised from ethanol. The compound synthesised was listed in the table.

IR: For compound (VIII) 3450 cm^{-1} ν(OH), 2950–3000 cm^{-1} ν(CH_2), 1700 cm^{-1} ν(C=O), 1590 cm^{-1} ν(C=N) and 1180–1140 cm^{-1} ν(C—O—C) and ν(C—S—C).

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