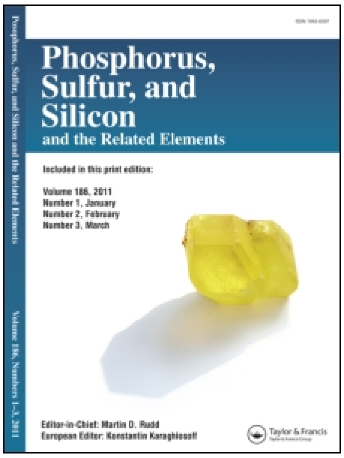

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SYNTHESIS OF 5,7-DIARYL PIPERIDINO[3,4-D]SELENA/THIADIAZOLES

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The title compounds 5,7-diaryl piperidino[3,4-d]selenadiazoles (**III**) & 5,7-diaryl piperidino[3,4-d]thiadiazoles (**IV**) have been prepared by the cyclization of semicarbazone derivatives of 4-piperidones (**II**) with selenium dioxide and thionyl chloride, respectively. The formation of the products were corroborated by spectral data.

Keywords: 4-piperidones; 4-piperidino semicarbazones; 1;2;3-selenadiazoles; 1;2;3-thiadiazoles; cyclization; condensation

INTRODUCTION

The incorporation of heteroatoms within a carbon frame often leads to new types of molecules which are sometimes biologically important. One such class of compounds are piperidones. The discovery of pethidine as a potential analgesic has stimulated great interest in the chemistry of piperidines.[1] Apart from this, piperidones and their derivatives serve as versatile building blocks for heterocyclic systems.[2] It is well known that a number of heterocyclic compounds containing nitrogen and sulfur possess different pharmacophoric properties. However, reports about selenium containing heterocycles are relatively scarce[3–5], although some of them are used as chemotherapeutic agents.[6] The present study therefore aims at the development of hitherto unknown selena and thia heterocycles with 4-piperidones as precursors.

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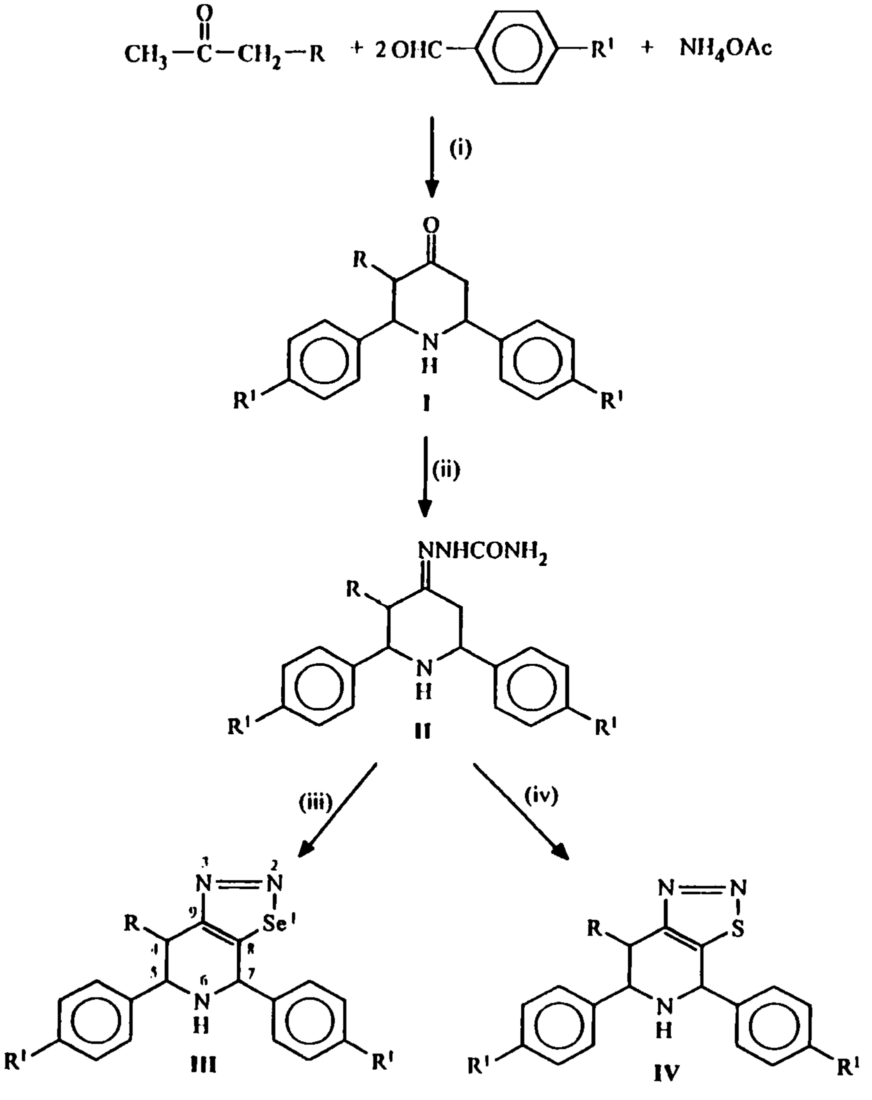
RESULTS AND DISCUSSION

The synthetic method involves building up of selenadiazole and thiadiazole rings on 4-piperidone. For this purpose 2,6-diaryl-3-alkyl/phenyl-4-piperidones (**I**) have been utilized as key intermediates. They are in turn prepared by the condensation of araldehydes with aliphatic ketones/benzyl methyl ketone and ammonium acetate in alcohol.[7] The selenadiazole ring was formed on piperidone by condensation of the latter with semicarbazide hydrochloride followed by cyclization with selenium dioxide in acetic acid. On the other hand, the cyclization of semicarbazone (**II**) with thionyl chloride in dichloromethane paved the way for the thiadiazole ring. Thus 5,7-diaryl piperidino[3,4-d]selenadiazoles (**III**) and 5,7-diaryl piperidino[3,4-d] thiadiazoles (**IV**) were made from *cis*-2,6-diaryl-3-alkyl/phenyl-4-piperidones (**I**) (see Scheme and Table I).

In **IIa**, having two substitutents at C_2 and C_6, the cyclization with SeO_2 and $SOCl_2$ is effective on both sides i.e., either at C_3 or at C_5 yielding the same type of product **IIIa** or **IVa**. However, in compounds **IIb–IIk**, where there is a substituent at C_3 cyclization with SeO_2 and $SOCl_2$ results in only one product. The ^1H NMR spectra of **IIIb–IIIk** indicates clearly that the products **III** and **IV** are formed by the cyclization of semicarbazones **IIb–IIk** with the methylene carbon (C_5).

The IR spectra (ν, cm^{-1}) of **II**, **III** and **IV** exhibited absorption bands in the region 3400–3450, indicating the presence of the NH group of piperidone[8]. The compounds **III** and **IV** displayed bands at 1440 and 600 due to N=N and C-S groups, respectively. The compound **II** showed bands in the regions 1682 and 3210 characteristic of a $CONH_2$ group.[8]

The PMR spectra (δ, ppm) of **IIa**, **IIIa** and **IVa** are taken as representative examples to relate spectral data to structures (see Table II). The spectrum of **IIa** displayed five distinct signals, a triplet at 2.10 (NH), two double doublets at 2.47 and 2.80 (H_a and H_e at C_3 & C_5), a multiplet in the region 3.85–4.00 (H_a at C_2 & C_6) and a singlet at 7.75 (NH_2). Furthermore, the -NH of semicarbazone moiety is merged with aromatic protons and appeared as multiplet in the region 6.90–7.35. The signals due to -NH and $-NH_2$ disappeared on deuteration. The δ_H values clearly indicates that the 2,6-diaryl-4-piperidino semicarbazone (**IIa**) exists in a chair conformation (see Fig 1) with the substituents at C_2 and C_6 being in equatorial positions thereby confirming *cis*-geometry. If **II** were to have a boat conformation, one may expect a close proximity of NH at position 1 and $>C=N-NHCONH_2$ at position 4. Thus, there would be a possibility of hydrogen bonding as shown in Fig. 2. Obviously this should lead to a broad singlet for the NH proton and a triplet for the methine protons at C_2 & C_6. However, the



(i) EtOH / Δ ; (ii) $H_2NNHCONH_2$ / NaOAc / MeOH / Δ ;

(iii) SeO_2 / AcOH / Δ 50-60° C ; (iv) $SOCl_2$ / CH_2Cl_2 / r.t.

TABLE I Melting points and analytical data of compounds II, III and IV

Compd.	*R*	*R'*	*Yield*	*m.p*	*Mol. formula*	*Found (Calcd.) (%)*		
No.			(%)	(°C)	*(mol.wt.)*	*C*	*H*	*N*
IIa	H	H	73	171–172[8]	$C_{18}H_{20}N_4O$ (308.38)	70.34 (70.10)	6.64 (6.53)	18.36 (18.16)
IIb	CH_3	H	79	191–192	$C_{19}H_{22}N_4O$ (322.41)	70.50 (70.78)	7.01 (6.87)	17.55 (17.37)
IIc	CH_3	CH_3	74	160–161	–	–	–	–
IId	CH_3	OCH_3	76	194–195	–	–	–	–
IIe	CH_3	Cl	75	180–181	–	–	–	–
IIf	CH_2CH_3	H	75	196–197	$C_{20}H_{24}N_4O$ (336.44)	71.12 (71.40)	7.07 (7.19)	16.48 (16.65)
IIg	$CH_2CH_2CH_3$	H	76	165–166	$C_{21}H_{26}N_4O$ (350.46)	72.12 (71.97)	7.39 (7.47)	15.89 (15.98)
IIh	$(CH_3)_2CH$	H	74	194–195	$C_{21}H_{26}N_4O$ (350.46)	72.10 (71.97)	7.51 (7.47)	15.92 (15.98)
IIi	$CH_2(CH_2)_2CH_3$	H	75	152–153	$C_{22}H_{28}N_4O$ (364.49)	72.31 (72.49)	7.85 (7.74)	15.46 (15.37)
IIj	$CH_2(CH_2)_3CH_3$	H	68	140–141	$C_{23}H_{30}N_4O$ (378.52)	73.14 (72.98)	7.91 (7.98)	14.69 (14.80)
IIk	C_6H_5	H	69	160–161	–	–	–	–
IIIa	H	H	44	112–113	$C_{17}H_{15}N_3Se$ (340.29)	59.85 (60.00)	4.49 (4.44)	12.46 (12.34)
IIIb	CH_3	H	47	105–106	$C_{18}H_{17}N_3Se$ (354.31)	61.16 (61.01)	4.91 (4.83)	11.79 (11.85)
IIIc	CH_3	CH_3	44	98–99	–	–	–	–
IIId	CH_3	OCH_3	48	118–119	–	–	–	–
IIIe	CH_3	Cl	47	98–99	–	–	–	–
IIIf	CH_2CH_3	H	44	70–71	$C_{19}H_{19}N_3Se$ (368.52)	61.81 (61.95)	5.25 (5.19)	11.33 (11.40)
IIIg	$CH_2CH_2CH_3$	H	43	95–96	–	–	–	–
IIIh	$(CH_3)_2CH$	H	44	82–83	$C_{20}H_{21}N_3Se$ (382.37)	62.94 (62.82)	5.50 (5.53)	10.85 (10.98)
IIIi	$CH_2(CH_2)_2CH_3$	H	46	89–90	–	–	–	–
IIIj	$CH_2(CH_2)_3CH_3$	H	43	80–81	–	–	–	–
IIIk	C_6H_5	H	43	98–99	$C_{23}H_{19}N_3Se$ (416.39)	66.43 (66.34)	4.52 (4.59)	10.24 (10.09)
IVa	H	H	44	150–151	$C_{12}H_{13}N_3S$ (293.39)	69.81 (69.59)	5.11 (5.15)	14.38 (14.32)
IVb	CH_3	H	46	122–123	$C_{18}H_{17}N_3S$ (307.42)	70.16 (70.32)	5.64 (5.57)	13.75 (13.66)
IVc	CH_3	CH_3	48	92–93	–	–	–	–
IVd	CH_3	OCH_3	47	86–87	–	–	–	–
IVe	CH_3	Cl	47	90–91	–	–	–	–
IVf	CH_2CH_3	H	43	98–99	$C_{19}H_{19}N_3S$ (321.44)	70.80 (70.99)	5.88 (5.95)	13.28 (13.07)
IVg	$CH_2CH_2CH_3$	H	42	82–83	$C_{20}H_{21}N_3S$ (335.47)	71.75 (71.60)	6.39 (6.30)	12.66 (12.52)

TABLE I (continued)

Compd. No.	*R*	*R'*	*Yield (%)*	*m.p (°C)*	*Mol. formula (mol. wt.)*	*Found (Calcd.) (%)*		
						C	*H*	*N*
IVh	$(CH_3)_2CH$	H	44	85–86	–	–	–	–
IVi	$CH_2(CH_2)_2CH_3$	H	46	77–78	$C_{21}H_{23}N_3S$ (349.50)	72.04 (72.16)	6.71 (6.63)	12.11 (12.02)
IVj	$CH_2(CH_2)_3CH_3$	H	43	73–74	–	–	–	–
IVk	C_6H_5	H	43	94–95	–	–	–	–

spectra of **II** run in $CDCl_3$ and DMSO-d_6 indicates a clear triplet for the NH proton and a multiplet for the H_a protons at C_2 and C_6. This clearly indicates a vicinal coupling interaction between -NH and H_a at C_2, -NH and H_a at C_6 (J = 10.6 cps)[9].

TABLE II PMR spectral data of II, III and IV

Compd. No.	*Chemical Shifts (δ, ppm in $CDCl_3$/DMSO-d_6)*
IIa	2.10 (t, 1H, NH), 2.47 (dd, 2H, H_a at C_3 & C_5), 2.80 (dd, 2H, H_e at C_3 & C_5), 3.85–4.00 (m, 2H, H_a at C_2 & C_6).
IIb	1.90 (t, 1H, NH), 2.18 (dd, 1H, H_a at C_5), 2.45–2.58 (m, 1H, H_a at C_3), 2.84 (dd, 1H, H_e at C_5) 3.62 (d, 1H, H_a at C_2), 3.82 (dd, 1H, H_a at C_6).
IIc	1.98 (t, 1H, NH), 2.12 (dd, 1H, H_a at C_5), 2.52–2.64 (m, 1H, H_a at C_3), 2.76 (dd, 1H, H_e at C_5), 3.48 (d, 1H, H_a at C_2), 3.76 (dd, 1H, H_a at C_6).
IId	2.00 (t, 1H, NH), 2.20 (dd, 1H, H_a at C_5), 2.50–2.60 (m, 1H, H_a at C_3), 3.00 (dd, 1H, H_e at C_5), 3.50 (d, 1H, H_a at C_2), 3.90 (dd, 1H, H_a at C_6).
IIe	2.10 (t, 1H, NH), 2.24 (dd, 1H, H_a at C_5), 2.52–2.64 (m, 1H, H_a at C_5), 3.84 (d, 1H, H_a at C_2), 3.96 (dd, 1H, H_a at C_6).
IIf	1.86 (t, 1H, NH), 2.26 (dd, 1H, H_a at C_5), 2.48–2.62 (m, 1H, H_a at C_3), 2.82 (dd, 1H, H_e at C_5), 3.71 (d, 1H, H_a at C_2), 3.84 (dd, 1H, H_a at C_6).
IIg	2.12 (t, 1H, NH), 2.20 (dd, 1H, H_a at C_5), 2.52–2.62 (m, 1H, H_a at C_3), 2.78 (dd, 1H, H_e at C_5), 3.58 (d, 1H, H_a at C_5), 3.78 (dd, 1H, H_a at C_6)
IIh	1.94 (t, 1H, NH), 2.18 (dd, 1H, H_a at C_5), 2.52–2.64 (m, 1H, H_a at C_3), 2.76 (dd, 1H, H_e at C_5), 3.64 (d, 1H, H_a at C_2), 3.80 (dd, 1H, H_a at C_6)
IIIa	1.30 (s, 1H, NH), 3.30–3.65 (m, 2H at C_4), 4.25 (d, 1H, at C_5), 5.40 (s, 1H, at C_7).
IIIb	1.72 (s, 1H, NH), 2.62–2.78 (m, 1H at C_4), 3.48 (d, 1H at C_5), 3.80 (s, 1H at C_7).
IIId	1.50 (s, 1H, NH), 2.50–2.75 (m, 1H at C_4), 3.55 (d, 1H at C_5), 4.00 (s, 1H at C_7).
IIIe	1.78 (s, 1H, NH), 2.76–2.90 (m, 1H at C_4), 3.54 (d, 1H at C_5), 4.20 (s, 1H at C_7).
IIIg	1.58 (s, 1H, NH), 2.62–2.74 (m, 1H at C_4), 3.32 (d, 1H at C_5), 3.96 (s, 1H at C_7).
IIIh	1.58 (s, 1H, NH), 2.62–2.74 (m, 1H at C_4), 3.36 (d, 1H at C_5), 3.92 (s, 1H at C_7).
IVa	1.30 (s, 1H, NH), 3.20–3.90 (m, 2H at C_4), 3.67 (d, 1H at C_5), 4.85 (s, 1H at C_7).
IVb	1.45 (s, 1H, NH), 2.62–2.75 (m, 1H at C_4), 3.54 (d, 1H at C_5), 3.82 (s, 1H at C_7).
IVc	1.38 (s, 1H, NH), 2.58–2.69 (m, 1H at C_4), 3.55 (d, 1H at C_5), 3.80 (s, 1H at C_7).
IVd	1.42 (s, 1H, NH), 2.56–2.70 (m, 1H at C_4), 3.48 (d, 1H at C_5), 3.76 (s, 1H at C_7).
IVh	1.40 (s, 1H, NH), 2.60–2.74 (m, 1H at C_4), 3.52 (d, 1H at C_5), 3.80 (s, 1H at C_7).
IVj	1.39 (s, 1H, NH), 2.58–2.70 (m, 1H at C_4), 3.54 (d, 1H at C_5), 3.82 (s, 1H at C_7).

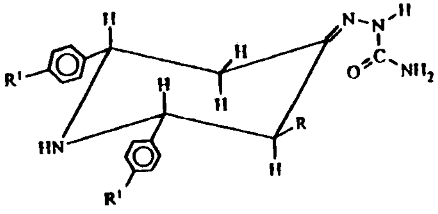


FIGURE 1

On the other hand **IIIa** and **IVa** exhibited four types of signals, a multiplet in the region 3.30–3.65 (CH_2 at C_4), a doublet at 4.25 (CH at C_5), a singlet at 5.40 (CH at C_7) and another singlet at 1.30 (NH). In **IIIa** and **IVa** the methylene protons at C_4 should appear either as a doublet or double doublet by interaction with the proton at C_5. However, a multiplet is observed in their spectra. In **IIIb–IIIk** and **IVb–IVk**, where there is a substituent at C_4, the methine proton at this position appeared as multiplet and a doublet was observed for the proton at C_5 contrary to **IIIa** and **IVa** (see Table II). The proton at C_7 appears at down field relative to the one at C_5 because of the deshielding effect of the adjacent double bond. Moreover, contrary to **II**, the spectra of **III** and **IV** indicates that there is no vicinal coupling of NH with adjacent protons at C_5 and C_7. This may be due to the rigidity of the piperidone ring system when it is fused with selenadiazole/thiadiazole moieties.

EXPERIMENTAL

Melting points were determined on Mel-Temp apparatus and are uncorrected. The purity of the compounds was checked by TLC (Silica gel H, BDH, ethyl acetate/hexane, 2:3). The IR spectra were recorded on a Perkin-Elmer Grating Infrared spectrophotometer Model 337 in KBr pellets. The ^1H NMR spectra were recorded in $CDCl_3$/DMSO-d_6 on a Bruker Spectrospin Varian EM-360 spectrophotometer with TMS as an internal standard. The micro analyses were performed by the University of Pune, Pune, India.

The piperidones were obtained by the condensation of araldehydes with appropriate ketones and ammonium acetate in alcohol.[7] The compounds were purified by recrystallization from ethanol. **Ia**, m.p: 102–103°C (lit[7] 104–105°C), **Ib**, m.p: 87–88°C (lit[7]: 86–87°C), **Ic**, m.p: 84–85°C, **Id**, m.p: 129–130°C, **Ie**,

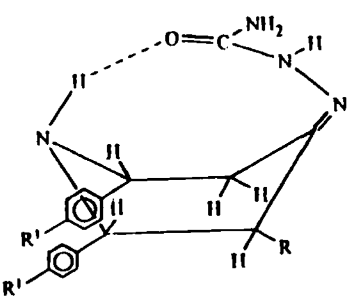


FIGURE 2

m.p: 70–71°C, **If**, m.p: 90–91°C (lit[7] 90–92°C), **Ig**, m.p: 89–90°C (lit[1], 91–92°C), **Ih**, m.p: 126–127°C (lit[7] 125–126°C), **Ii**, m.p: 88–89°C (lit[1] 89–90°C), **Ij**, m.p: 98–99°C, **Ik**, m.p: 102–103°C.

General Procedure for the Preparation of 2,6-diaryl-4-piperidinosemicarbazone (II)

A mixture of semicarbazide hydrochloride (10 mmol) and sodium acetate trihydrate (20 mmol) was dissolved in methanol (30 ml) and the residue (NaCl) formed was filtered off. To the filtrate the appropriate compound **I** (5 mmol) in methanol was added and the reaction mixture was heated to reflux for 2–4 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the contents were concentrated and poured into ice-cold water. The solid obtained was washed with water, dried and recrystallized from ethanol to obtain pure **II**.

General Procedure for the Preparation of 5,7-diaryl piperidino[3,4-d]selenadiazole (III)

The appropriate semicarbazone **II** (0.65 mmol) was dissolved in glacial acetic acid (15 ml) and warmed gently with stirring. To this, selenium dioxide (0.65 mmol) was added portion-wise during a period of 0.5 h and the stirring was continued for 2–3 h till the evolution of gas ceased. After completion of the reaction, the mixture was filtered to remove deposited selenium. The filtrate was poured onto crushed ice and the solid which separated was washed thoroughly with cold water and sodium bicarbonate. The resultant compound was purified on a column of silica gel (60–120 mesh, BDH) with ethyl acetate/hexane (2:3) as eluants.

General Procedure for the Preparation of 5,7-diaryl piperidino[3,4-d]thiadiazole (IV)

The appropriate compound **II** (10 mmol) was added portion-wise to an excess of thionyl chloride (5 ml) at 0°C. The mixture was then allowed to attain room temperature. After 1 h, methylene chloride (10–15 ml) was added and the resulting mixture was decomposed with saturated sodium carbonate solution. The methylene chloride layer was washed thoroughly with water and dried over anhydrous sodium sulfate. Evaporation of the solvent gave the crude product which was purified by column chromatography using silica gel (60–120 mesh, BDH) with ethylacetate/hexane (2:3) as eluants.

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