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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 scarce³⁻⁵, 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 SeO₂ and SOCl₂ 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 SeO₂ and SOCl₂ 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 piperidone⁸. 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 CONH₂ 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 C₃ & C₅), a multiplet in the region 3.85–4.00 (H_a at C₂ & C₆) and a singlet at 7.75 (NH₂). 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 -NH₂ disappeared on deuteration. The $\delta_{\rm H}$ values clearly indicates that the 2,6-diaryl-4-piperidino semicarbazone (IIa) exists in a chair conformation (see Fig 1) with the substituents at C₂ and C₆ 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-NHCONH₂ 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 C₂ & C₆. However, the



(i) EtOH / Δ ; (ii) H₂NNHCONH₂ / NaOAc / MeOH / Δ ; (iii) SeO₂ / AcOH / Δ 50-60° C; (iv) SOCl₂ / CH₂Cl₂ / r.t.

Compd.	R	R ¹	Yield	m.p	Mol. formula	Found (Calcd.) (%)		
No.			(%)	(°C)	(mol.wt.)	С	H	N
Ha	н	Н	73	171–172 ⁸	$C_{18}H_{20}N_4O$ (308-38)	70.34	6.64 (6.53)	18.36
IIb	CH ₃	Н	79	191–192	$C_{19}H_{22}N_4O$ (322.41)	70.50	(0.55) 7.01 (6.87)	17.55
IIc	CH ₃	CH ₃	74	160-161	-	-	-	-
IId	CH ₃	OCH ₃	76	194-195	-	-	-	_
IIe	CH ₃	Cl	75	180-181	-	-		-
llf	CH ₂ CH ₃	н	75	196–197	C ₂₀ H ₂₄ N ₄ O (336.44)	71.12 (71.40)	7.07 (7.19)	16.48 (16.65)
IIg	CH ₂ CH ₂ CH ₃	н	76	165-166	$C_{21}H_{26}N_4O$ (350.46)	72.12	7.39	15.89 (15.98)
IIh	(CH ₃) ₂ CH	н	74	194–195	$C_{21}H_{26}N_4O$ (350.46)	72.10	7.51	15.92
Ili	CH ₂ (CH ₂) ₂ CH ₃	н	75	152-153	$C_{22}H_{28}N_4O$	72.31	7.85	15.46
IIj	CH ₂ (CH ₂) ₃ CH ₃	Н	68	140–141	$C_{23}H_{30}N_4O$ (378 52)	73.14	7.91	14.69
IIk	C.H.	н	69	160-161	-	-	_	_
IIIa	H	Н	44	112–113	C ₁₇ H ₁₅ N ₃ Se (340.29)	59.85 (60.00)	4.49 (4.44)	12.46 (12.34)
HIb	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 ₂	CH ₁	44	98-99	-	-	_	_
IIId	CH	OCH ₁	48	118-119	_	_		-
IIIe	CH	CI	47	9899	-	_	-	-
IIIf	CH ₂ CH ₃	Н	44	70–71	C ₁₉ H ₁₉ N ₃ Se (368.52)	61.81 (61.95)	5.25 (5.19)	11.33 (11.40)
IIIg	CH ₂ CH ₂ CH ₃	н	43	95-96	-	-	_	_
IIIĥ	(CH ₃) ₂ CH	Н	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) ₂ CH ₃	н	46	89-90	-	_	_	_
IIIj	CH ₂ (CH ₂) ₃ CH ₃	н	43	80-81	-	-	-	-
IIIk	C ₆ H ₅	н	43	98–99	C ₂₃ H ₁₉ N ₃ Se (416.39)	66.43 (66.34)	4.52 (4.59)	10.24 (10.09)
IVa	н	н	44	150-151	C ₁₂ H ₁₃ N ₃ S (293.39)	69.81 (69.59)	5.11 (5.15)	14.38 (14.32)
IVb	CH3	Н	46	122-123	C ₁₈ H ₁₇ N ₃ S (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	8687	_	_	-	-
I Ve	CH ₃	Cl	47	90-91	-	-	-	-
IVf	CH ₂ CH ₃	н	43	98–99	C ₁₉ H ₁₉ N ₃ S (321.44)	70.80 (70.99)	5.88 (5.95)	13.28 (13.07)
IVg	CH ₂ CH ₂ CH ₃	Н	42	82–83	C ₂₀ H ₂₁ N ₃ S (335.47)	71.75 (71.60)	6.39 (6.30)	12.66 (12.52)

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

Compd.	R	R'	Yield (%)	т.р (°С)	Mol. formula (mol. wt.)	Found (Calcd.) (%)		
	No.					С	H	N
IVh	(CH ₃) ₂ CH	Н	44	85-86		_	-	-
IVi	CH ₂ (CH ₂) ₂ CH ₃	Н	46	7778	$C_{21}H_{23}N_3S$	72.04	6.71	12.11
IVj	CH ₂ (CH ₂) ₂ CH ₂	н	43	73-74	(349.30)	(72.10)	(0.03)	(12.02)
IVk	C ₆ H ₅	н	43	94-95	_	_	_	_

TABLE I (continued)

spectra of II run in CDCl₃ and DMSO-d₆ indicates a clear triplet for the NH proton and a multiplet for the H_a protons at C₂ and C₆. This clearly indicates a vicinal coupling interaction between -NH and H_a at C₂, -NH and H_a at C₆ (J = $10.6 \text{ cps})^9$.

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 ₄).
IIb	1.90 (t, 1H, NH), 2.18 (dd, 1H, H _a at C_3), 2.45–2.58 (m, 1H, H _a at C_3), 2.84 (dd, 1H, H _e at C_3) 3.62 (d, 1H, H _a at C_5), 3.82 (dd, 1H, H _a at C_5)
llc	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_5)
lld	2.00 (t, 1H, NH), 2.20 (dd, 1H, H _a at C ₃), 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 ₂).
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).
llf	1.86 (t, 1H, NH), 2.26 (dd, 1H, H _a at C ₃), 2.48–2.62 (m, 1H, H _a at C ₃), 2.82 (dd, 1H, H _e at C ₃), 3.71 (d, 1H, H _a at C ₂), 3.84 (dd, 1H, H _a at C ₄).
llg	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)
llh	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 IIIb	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). 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 IIIe	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). 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 IIIh	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). 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 IVb	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). 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 IVd	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). 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 ∣ IVj ∣	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). 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 (CH₂ at C₄), a doublet at 4.25 (CH at C₅), a singlet at 5.40 (CH at C₇) and another singlet at 1.30 (NH). In IIIa and IVa the methylene protons at C₄ should appear either as a doublet or double doublet by interaction with the proton at C₅. However, a multiplet is observed in their spectra. In IIIb-IIIk and IVb-IVk, where there is a substituent at C₄, the methine proton at C₅ contrary to IIIa and IVa (see Table II). The proton at C₇ appears at down field relative to the one at C₅ 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 C₅ and C₇. 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 CDCl₃/DMSO-d₆ 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 (lit⁷ 104–105°C), Ib, m.p: 87–88°C (lit⁷: 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 (lit⁷ 90–92°C), **Ig**, m.p: 89–90°C (lit¹, 91– 92°C), **Ih**, m.p: 126–127°C (lit⁷ 125–126°C), **Ii**, m.p: 88–89°C (lit¹ 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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