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SYNTHESIS OF N-(PHENOXATHIIN-2-CARBONYL)- OR N-(THIANTHRENE-2-CARBONYL)-N'-ARYLTHIOUREAS

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The reactions of phenoxathiin-2-carbonyl- or thianthrene-2-carbonyl-isothiocyanates with certain primary amines lead to the formation of corresponding N'-substituted-N-hetaroylthiocarbamides. The aforementioned isothiocyanates were obtained in situ by reactions of phenoxathiin-2- or thianthrene-2-carbonyl chlorides with KSCN. The new compounds were characterized by elemental analysis and spectral data (IR, ^1H and ^{13}C NMR).

The N'-substituted-N-aroylthiocarbamides are known as intermediates suitable for further cyclization, yielding a variety of heterocyclic derivatives, analytical reagents, and biologically active compounds [1-4]. On the other hand, polynuclear derivatives (e.g., phenothiazine, acridine, phenazine, phenoxathiin) show a large variety of interesting biological activities, some drugs belonging to this category of compounds [5-8].

In this paper we describe the synthesis and characterization of some new N-(phenoxathiin-2-carbonyl)- or N-(thianthrene-2-carbonyl)-N'-arylthioureas (I-XIV), which were obtained by reaction of phenoxathiin-2- or thianthrene-2-carbonyl chlorides with KSCN and the addition of some primary amines to the intermediate N-(phenoxathiin-2-carbonyl) or N-(thianthrene-2-carbonyl)isothiocyanate (Scheme).

All the new compounds were characterized by elemental analyses and IR, ^1H and ^{13}C NMR spectral data.

The ^1H NMR spectra (Table 1) are in perfect agreement with the structures of all new compounds. The ^{13}C NMR spectra, including bidimensional connectivity experiments (^1H-^{13}C-, ^1H-^1H-, and ^{13}C-^{13}C-COSY) [9] permitted a better characterization of the new compounds. The positions of ^{13}C NMR signals are presented in Table 2.

EXPERIMENTAL

IR spectra (KBr pellets) were recorded on an FTS 135 Biorad instrument (Table 3) and the NMR spectra on a Jeol-LAMBDA 400 spectrometer (400 MHz for ^1H and 100 MHz for ^{13}C, using TMS as internal standard). Melting points were determined on a Boetius apparatus and are uncorrected. Thin layer chromatography was carried out on silica gel Merck plates using an unidimensional technique and the development was done with petroleum ether–toluene–acetone–methanol, 5:3.5:1:0.5. Visualization was done with a UV lamp (254 nm) or conc. H_2SO_4.

Phenoxathiin-2- and thianthrene-2-carbonyl chlorides were obtained according to literature data [10, 11].

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TABLE 1. ^{1}H-Chemical Shifts

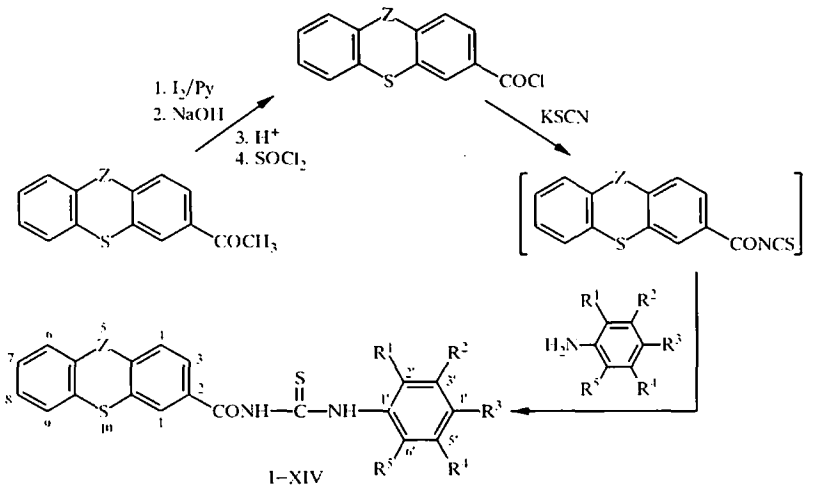
Compound	δ_H (ppm), J (Hz)													
	H-1	H-3	H-4	H-9	H-6	H-8	H-7	H-2'	H-3'	H-4'	H-5'	H-6'	CONH CSNH	Others
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
I	7.92 d, J_{12} = 1.9	7.83 dd, J_{34} = 8.8 J_{31} = 2.1	7.21 d, J_{43} = 8.7	7.29 d, J_{98} = 7.5	7.11-7.15 (m, 2H)		7.25 t, J_{78} = 7.3 J_{76} = 7.1	8.05 d, $J_{2'3'}$ = 8.8	8.26 d, $J_{3'2'}$ = 8.8	—	8.26 d, $J_{5'6'}$ = 8.8	8.05 d, $J_{6'5'}$ = 8.8	11.75 12.77	—
II	8.20 d, J_{13} = 1.9	7.94 dd, J_{34} = 8.0; J_{31} = 1.8	7.77 d, J_{43} = 8.0	7.64-7.68 m, 2H			7.42-7.47 m, 2H	8.12d, $J_{2'3'}$ = 9.1	8.33 d, $J_{3'2'}$ = 9.0	—	8.33 d, $J_{5'6'}$ = 9.0	8.12 d, $J_{6'5'}$ = 9.1	11.93 12.80	—
III	7.93 d, J_{13} = 2.1	7.83 dd, J_{34} = 8.5 J_{31} = 2.1	7.20 d, J_{43} = 8.5	7.28 d, J_{98} = 7.8	7.11-7.15 (m, 2 H)		7.24 t, J_{78} = 7.8 J_{76} = 7.4	—	7.59 d, $J_{3'5'}$ = 2.4	—	7.36 dd, $J_{5'6'}$ = 8.8; $J_{5'3'}$ = 2.5	7.75 d, $J_{6'5'}$ = 8.9	11.78 12.55	3.87 s, OCH_3
IV	8.13 s	7.89 d, J_{34} = 8.0	7.76 d, J_{43} = 8.1	7.56-7.59 m, 2H			7.33-7.39 m, 2H	—	7.58 d, $J_{3'5'}$ = 2.8	—	7.34 dd, $J_{5'6'}$ = 8.8; $J_{5'3'}$ = 2.8	7.76 d, $J_{6'5'}$ = 8.8	11.93 12.57	3.86 s, OCH_3
V	7.93 d, J_{13} = 2.1	7.83 dd, J_{34} = 8.5; J_{31} = 2.1	7.18 d, J_{43} = 8.4	7.26 d, J_{98} = 7.8	7.12-7.14 m, 2H		7.24 t, J_{78} = 7.8 J_{76} = 7.5	—	—	7.10-7.2 m, 2H		7.28 d, $J_{6'5'}$ = 6.3	11.57 12.13	2.18 (CH_3); 2.33 (CH_3)
VI	8.21 s	7.95 dd, J_{34} = 8.0; J_{31} = 1.4	7.76 d, J_{43} = 8.0	7.64-7.67 m, 2H			7.42-7.46 m, 2H	—	—	7.17-7.18 m, 2H		7.32 t, $J_{6'5'}$ = 9.0; $J_{6'4'}$ = 4.2	11.78 12.17	2.18 (CH_3); 2.32 (CH_3)
VII	7.92 d, J_{13} = 2.2	7.82 dd, J_{34} = 8.5; J_{31} = 2.2	7.19d, J_{43} = 8.5	7.28 dd, J_{98} = 7.7; J_{97} = 1.5	7.12-7.14 m, 2H		7.24 td, J_{78} = 7.8; J_{76} = 7.5; J_{79} = 1.6	—	7.09 d, $J_{3'5'}$ = 1.5	—	7.02 dd, $J_{5'6'}$ = 8.1; $J_{5'3'}$ = 1.6	7.40 d $J_{6'5'}$ = 8.0	11.57 12.15	2.19 (CH_3); 2.27 (CH_3)

TABLE 1(continued)

1	2	3	4	5	6	7	8	9	10	11	12	13	14
VIII	7.93 d, J_{13}= 2.1	7.84 dd, J_{34} = 8.5; J_{31} = 2.1	7.19 d, J_{43} = 8.5	7.27 dd, J_{98} = 7.7; J_{97} = 1.7	7.12-7.16 m, 2H	7.24 td, J_{78} = 7.8; J_{76} = 7.6; J_{79} = 1.7	—	7.11 d, J_{yx} = 7.5	7.03 dd, J_{xy} = 7.5; J_{xw} = 1.5	—	7.15d, J_{wx} =1.4	11.45 12.15	2.20 (CH_3); 2.28 (CH_3)
IX	7.95 d, J_{13} = 2.2	7.84 dd, J_{34} = 8.5; J_{31} = 2.2	7.19 d, J_{43} = 8.5	7.28 dd, J_{98}= 7.1; J_{97} = 1.5	7.12-7.14 m, 2H	7.24 td, J_{78} = 7.8; J_{76} = 7.6; J_{79} = 1.5	—		7.09-7.11 m, 3H		—	11.59 11.79	2.28 (CH_3); 2.28 (CH_3)
X	7.90 d, J_{13} = 2.0	7.80 dd, J_{34} = 8.4; J_{31} = 2.0	7.19 d, J_{43} = 8.5	7.28 dd, J_{98} = 7.7; J_{97} = 1.5	7.12-7.14 m, 2H	7.24 td, J_{78} = 7.8; J_{76} = 7.6; J_{79} = 1.5	7.38 d, J_{56} = 2.2	—	—	7.15 d, J_{56} = 8.0	7.41 dd, J_{65} = 8.0; J_{62} = 2.2	11.49 12.46	2.20 (CH_3); 2.21 (CH_3)
XI	7.95 d, J_{13} = 2.0	7.85 dd, J_{34} = 8.5; J_{31} = 2.1	7.19 d, J_{43} = 8.5	7.28 dd, J_{98} = 7.8; J_{97} = 1.5	7.15-7.18 m, 2H	7.24 td, J_{78} = 7.8; J_{76} = 7.6; J_{79} = 1.4	—		7.11-7.13 m, 3H		—	11.60 11.85	2.19 (CH_3); 2.52 ($C\underline{H}_2CH_3$); 1.13 ($CH_2C\underline{H}_3$)
XII	7.90 d, J_{13} = 2.2	7.80 dd, J_{34} = 8.5; J_{31} = 2.2	7.19 d, J_{43} = 8.5	7.28 dd, J_{98} = 7.8; J_{97} = 1.4	7.11-7.15 m, 2H	7.24 td, J_{78} = 7.9; J_{76} = 7.7; J_{79} = 1.5;	7.52 d, J_{yx} = 8.7	6.95 d, J_{yz} = 8.7	—	6.95 d, J_{56} = 8.7	7.52 d, J_{65} = 8.7	11.49 12.37	3.76 (OCH_3)
XIII	7.89 s	7.80 d, J_{34} = 8.4	7.19 d, J_{43} = 8.5	7.27 d, J_{98} = 7.7	7.10-7.14 m, 2H	7.24 t, J_{78} = 7.8 J_{76} = 7.6	7.58 d, J_{yx} = 8.3	7.63 d, J_{yz} = 8.4	—	7.63 d, J_{56} = 8.4	7.58 d, J_{65} = 8.3	11.72 12.75	—
XIV	7.91 d, J_{13} = 2.2	7.81 dd, J_{34} = 8.5; J_{31} = 2.2	7.21 d, J_{43} = 8.5	7.29 dd, J_{98} = 7.8; J_{97} = 1.5	7.12-7.14 m, 2H	7.25 td, J_{78} = 7.9; J_{76} = 7.6; J_{79} = 1.4	7.69 d, J_{yx} = 8.8	7.84 d, J_{yz} = 8.8	—	7.84 d, J_{56} = 8.8	7.69 d, J_{65} = 8.8	11.64 12.55	—

TABLE . ^{13}C-Chemical Shifts (δ_C, ppm)

Com-pound	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
C-1	127.77	128.46	127.81	128.60	127.73	128.65	127.73	127.76	127.76	127.62	127.77	127.59	127.11	127.82
C-2	128.63	133.30	129.54	133.20	128.65	132.52	128.74	128.68	128.62	128.69	128.60	128.65	128.62	128.91
C-3	129.55	128.55	131.26	128.50	129.43	128.35	129.43	129.46	129.44	129.42	129.47	129.38	129.47	131.48
C-4	117.62	131.69	117.58	133.30	117.52	131.91	117.53	117.56	117.55	117.59	117.54	117.56	117.60	118.58
C-4a	154.65	140.40	154.63	140.45	154.52	140.22	154.51	154.55	154.51	154.52	154.51	154.59	154.61	156.89
C-5a	150.32	134.30	150.36	133.57	150.36	133.63	150.38	150.39	150.36	150.36	150.35	150.36	150.38	151.33
C-6	117.87	128.84	117.85	128.80	117.83	128.97	117.85	117.88	117.85	117.84	117.85	117.79	117.88	118.72
C-7	128.53	128.63	128.59	128.60	128.57	128.56	128.59	128.61	128.58	127.67	128.58	128.60	127.72	127.95
C-8	125.67	128.63	125.64	128.60	125.62	128.56	125.63	125.66	125.63	125.64	125.64	125.56	125.67	125.88
C-9	127.11	128.84	127.10	128.80	127.08	128.90	127.10	127.11	127.10	127.13	127.67	127.11	126.51	127.16
C-9a	119.25	134.30	119.24	133.57	119.18	133.62	119.18	119.22	119.19	119.18	119.18	119.17	119.24	122.40
C-10a	118.04	138.40	118.08	134.40	118.10	134.34	118.11	118.22	118.11	118.07	118.11	118.06	118.08	118.87
C-1'	144.31	144.32	124.90	124.80	137.23	137.23	136.27	136.71	136.27	135.56	140.48	130.78	137.41	139.61
C-2'	123.96	124.25	125.64	144.97	132.46	133.37	134.40	130.31	135.07	125.17	135.32	125.90	118.61	126.08
C-3'	124.32	123.95	119.88	109.15	136.83	136.81	130.92	130.26	127.88	136.56	127.92	113.80	131.52	122.57
C-4'	144.00	143.93	157.78	157.90	124.80	125.44	126.40	126.95	127.42	134.43	126.19	157.41	118.55	127.46
C-5'	124.32	123.95	109.11	119.80	125.44	128.41	126.65	135.31	127.88	129.57	127.09	113.80	131.52	122.57
C-6'	123.96	124.25	144.93	128.50	119.18	124.79	133.10	127.76	135.07	121.57	135.60	125.90	118.61	126.08
C=O	166.49	166.69	166.61	166.90	166.60	166.95	166.86	166.65	166.28	165.26	166.41	166.50	166.49	166.13
C=S	179.13	179.09	181.04	181.00	180.29	180.20	180.23	179.87	180.14	178.17	180.53	179.01	179.19	179.63
others			59.73 (OCH_3)	56.10 (OCH_3)	20.01 (CH_3)	13.97 (CH_3)	17.58 (CH_3)	17.27 (CH_3)	17.87 ($2CH_3$)	19.42 (CH_3)	14.51 ($CH_2\underline{CH_3}$)	55.24 (OCH_3)	—	—
					20.76 (CH_3)	19.97 (CH_3)	20.57 (CH_3)	20.53 (CH_3)		19.86 (CH_3)	17.95 (CH_3)			
											24.26 ($\underline{CH_2}CH_3$)			



	Z	R^1	R^2	R^3	R^4	R^5
I	O	H	H	NO_2	H	H
II	S					
III	O	NO_2	H	OCH_3	H	H
IV	S					
V	O	CH_3	CH_3	H	H	H
VI	S					
VII	O	CH_3	H	CH_3	H	H
VIII	O	CH_3	H	H	CH_3	H
IX	O	CH_3	H	H	H	CH_3
X	O	H	CH_3	CH_3	H	H
XI	O	CH_3	H	H	H	C_2H_5
XII	O	H	H	OCH_3	H	H
XIII	O	H	H	Br	H	H
XIV	O	H	H	SCN	H	H

TABLE 3. IR Spectral Characteristics of the Synthesized Compounds I-XIV

Compound	ν (cm^{-1})						
	CH_3 (*as*)	CH_3 (*sym*)	(CO)-NH	C=O	C–O–C (*as*)	C–O–C (*sym*)	Others
I			3244.3	1665.2	1265	1111	1519.5 (NO_{2as}); 1328.6 (NO_{2sym})
II	—	—	3263.9	1670.3	—	- -	1514.1 (NO_{2as}); 1321.7 (NO_{2sym})
III	2923.2	2850.6	3254.7	1683.8	1265.1	1031.2	1520.7 (NO_{2as}); 1351.4 (NO_{2sym})
IV	2923.8	2853.1	3418.9	1681.3	—	-	1519.3 (NO_{2as}); 1322.2 (NO_{2sym})
V	2938.1	2856.5	3209.9	1667.7	1256.9	1089.3	—
VI	2923.8	2855.1	3218.5	1672.4	—	—	—
VII	2920.7	2860.7	3265.2	1667.4	1248.6	1088.7	—
VIII	2920.3	2862.1	3386.2	1668.3	1211.2	1087.1	—
IX	2919.2	2851.1	3199.9	1665.7	1249.1	1089.3	—
X	2969.1	2920.9	3265.8	1667.7	1293.2	1087.8	—
XI	2934.2	2873.1	3194.5	1666.7	1249.8	1090.3	—
XII	2965.4	2835.2	3246.4	1666.3	1242.4	1031.8	—
XIII	—	—	3236.7	1667.3	1266.4	1074.1	824.1; 740.2 (C–Br)
XIV	—	—	3266.5	1672.5	1199.4	1063.2	2163.2 (NCS)

TABLE 4. Characteristics of the Synthesized Compounds I-XIV

Compound	Empirical formula	Found, % / Calculated, %		mp, °C	Yield, %
		N	S		
I	$C_{21}H_{13}N_3O_4S_2$	9.68 / 9.92	14.92 / 15.14	218-219	86.3
II	$C_{20}H_{13}N_3O_3S_3$	9.21 / 9.56	21.53 / 21.88	199-201	69.2
III	$C_{21}H_{15}N_3O_5S_2$	9.41 / 9.27	14.33 / 14.12	183-184	78.3
IV	$C_{21}H_{15}N_3O_4S_3$	8.53 / 8.94	20.12 / 20.48	110-112	71.4
V	$C_{22}H_{18}N_2O_2S_2$	6.43 / 6.89	15.61 / 15.77	199-200	78.7
VI	$C_{22}H_{18}N_2OS_3$	6.38 / 6.63	22.59 / 22.76	158-159	53
VII	$C_{22}H_{18}N_2O_2S_2$	6.51 / 6.89	15.42 / 15.77	176-177	68.7
VIII	$C_{22}H_{18}N_2O_2S_2$	6.49 / 6.89	15.38 / 15.77	169-171	79.6
IX	$C_{22}H_{18}N_2O_2S_2$	6.57 / 6.89	15.31 / 15.77	205-206	79
X	$C_{22}H_{18}N_2O_2S_2$	6.72 / 6.89	15.46 / 15.77	197-198	85.9
XI	$C_{23}H_{20}N_2O_2S_2$	6.41 / 6.66	15.11 / 15.24	212-213	84.3
XII	$C_{21}H_{16}N_2O_2S_2$	6.73 / 6.85	15.29 / 15.69	197-198	74.8
XIII	$C_{20}H_{13}N_2O_2S_2$	5.97 / 6.12	13.87 / 14.02	215-216	77.1
XIV	$C_{21}H_{13}N_3O_2S_3$	9.48 / 9.60	21.93 / 22.08	187-188	78

General Procedure for the Preparation of N-(Phenoxathiin-2-carbonyl)- or N-(Thianthrene-2-carbonyl)-N'-arylthioureas (I-XIV). To a solution of potassium thiocyanate (0.35 g, 3.6 mmol) in warm anhydrous acetone (10 ml) a solution of hetaroyl chloride (3.6 mmol) in acetone (40 ml) was added dropwise and the resulting mixture was refluxed for 10 minutes. After a solution of substituted aniline (3.6 mmol) in acetone (10 ml) was slowly added, the suspension was refluxed with stirring for an additional 2 hours. The reaction mixture was poured into water (100 ml) and the precipitate was filtered off and recrystallized from 1-butanol. Characteristics of thioureas I-XIV are presented in Table 4.

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