Synthesis and Spectroscopic Properties of Some New *N,N'*-Disubstituted Thioureas of Potential Biological Interest

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Thirty-six new *N,N'*-disubstituted thioureas have been synthesized by the reaction of phenyl-, *p*-fluorophenyl- and benzoylisothiocyanates with various substituted anilines, aminopyridines and 4-aminoquinolines. The uv, ir and nmr spectral data are presented and discussed.

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A large number of *N,N'*-diarylthioureas were synthesized by Buu-Hoi, *et al* and were reported to show tuberculostatic activity and inhibitory properties against influenza virus [1]. They also found that all the diarylthioureas described presented chelating properties towards heavy metals and a link between this property and biological activity have been suggested [2]. A number of thiourea derivatives have reported to exhibit marked antituberculous, antibacterial and fungicidal activities [3-6]. Significant insecticidal and acaricidal activities have also been reported

Table 1

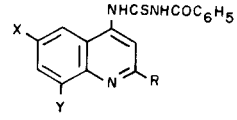
Physical Properties of *N,N'*-Disubstituted Thioruea Derivatives [a]
RNHCONHR'

Compound No.	R	R'	Molecular Formula	Mp °C	Yield %	Reaction Medium	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
1	2-Pyridyl	*p*-F-Phenyl	$C_{12}H_{10}N_3SF$	173-174	71	Ethanol	58.28	4.08	17.06	58.32	4.02	17.11
2	2-Pyridyl	Phenyl	$C_{12}H_{11}N_3S$	171-172	75	Benzene	62.85	4.83	18.40	62.79	4.78	18.36
3	2,6-Di-Cl-3-pyridyl	Benzoyl	$C_{13}H_9Cl_2N_3OS$	183-185	70	Benzene	47.88	2.78	12.88	47.62	2.74	12.84
4	5-Cl-2-Pyridyl	Benzoyl	$C_{13}H_{10}ClN_3OS$	148-149	90	Acetone	53.51	3.45	14.46	53.44	3.39	14.44
5	2-Pyridyl	Benzoyl	$C_{13}H_{11}N_3OS$	137-138	91	Benzene	60.60	4.30	16.40	60.56	4.26	16.48
6	3-Pyridyl	Benzoyl	$C_{13}H_{11}N_3OS$	165-166	86	Benzene	60.68	4.30	16.40	60.68	4.27	16.40
7	4-Me-2-Pyridyl	Phenyl	$C_{13}H_{13}N_3S$	157-159	86	Benzene	64.12	5.38	17.33	64.36	5.33	17.37
9	4-Me-2-Pyridyl	Benzoyl	$C_{14}H_{13}N_3OS$	154-155	77	Benzene	61.97	4.82	15.55	62.08	4.82	15.60
10	6-Me-2-Pyridyl	Benzoyl	$C_{14}H_{13}N_3OS$	141-142	65	Benzene	61.97	4.82	15.55	61.95	4.80	15.69
11	6-MeO-3-Pyridyl	Benzoyl	$C_{14}H_{13}N_3O_2S$	130-131	70	Benzene	58.52	4.56	14.68	58.52	4.63	14.67
12	$C_6H_5CONHCSNH$-2,6-Pyridyl	Benzoyl	$C_{21}H_{17}N_5O_2S_2$	207-208	79	Acetone	57.91	3.93	16.14	57.83	3.89	16.27
13	Phenyl	Phenyl	$C_{13}H_{12}N_2S$	153-154	89	Benzene	68.39	5.29	12.32	68.37	5.26	12.35
14	2,4,6-trichlorophenyl	Benzoyl	$C_{14}H_9Cl_3N_2OS$	195-196	72	Benzene	46.75	2.52	7.82	46.60	2.56	7.82
15	2-Chlorophenyl	Benzoyl	$C_{14}H_{11}ClN_2OS$	143-144	59	Ethanol	57.83	3.81	9.67	58.02	3.75	9.59
16	3-Chlorophenyl	Benzoyl	$C_{14}H_{11}ClN_2OS$	124-125	58	Ethanol	57.83	3.81	9.67	57.90	3.79	9.62
17	4-Chlorophenyl	Benzoyl	$C_{14}H_{11}ClN_2OS$	138-139	79	Ethanol	57.83	3.81	9.67	57.91	3.90	9.76
18	2-Nitrophenyl	Benzoyl	$C_{14}H_{11}N_3O_3S$	146-147	88	Ether	55.77	3.68	13.99	55.84	3.63	13.91
19	3-Nitrophenyl	Benzoyl	$C_{14}H_{11}N_3O_3S$	160-161	82	Methanol	55.77	3.68	13.99	56.01	3.68	13.95
20	4-Nitrophenyl	Benzoyl	$C_{14}H_{11}N_3O_3S$	182-183	62	Methanol	55.77	3.68	13.99	55.94	3.68	14.19
21	Phenyl	Benzoyl	$C_{14}H_{11}N_2OS$	143-144	80	Benzene	65.60	4.71	10.97	65.46	4.66	10.80
22	2-MeO-4-nitrophenyl	Benzoyl	$C_{15}H_{13}N_3O_4S$	205-206	71	Ethanol	54.34	3.95	12.73	54.53	3.95	12.99
23	2-MeO-phenyl	Benzoyl	$C_{15}H_{14}N_2O_2S$	150-151	72	Benzene	62.91	4.92	9.82	62.91	4.88	9.75
24	4-Acetamidophenyl	Benzoyl	$C_{16}H_{15}N_3O_2S$	199-200	91	Ether	61.29	4.82	13.46	61.56	4.84	13.73
25	4-Ethoxyphenyl	Benzoyl	$C_{16}H_{16}N_2O_2S$	146-147	78	Ethanol	63.98	5.37	9.36	64.16	5.37	9.32
26	2,4,5-Tri-MeO-phenyl	Benzoyl	$C_{17}H_{18}N_2O_4S$	157-158	67	Benzene	58.94	5.23	8.12	59.09	5.27	7.97
27	4-*N,N*-Diethylaminophenyl	Benzoyl	$C_{18}H_{21}N_3OS$	129-130	73	Benzene	65.98	6.46	12.88	65.97	6.47	12.78
28	$C_6H_5N{=}N\text{-}C_6H_4$-*p*	Benzoyl	$C_{20}H_{16}N_4OS$	198-199	88	Ethanol	66.60	4.47	15.60	66.81	4.44	15.57
29	$C_6H_5CONHCSNH\text{-}C_6H_4$-*o*	Benzoyl	$C_{22}H_{18}N_4O_2S_2$	178-179	83	Ethanol	60.81	4.17	12.92	60.77	4.16	12.97
30	$C_6H_5CONHCSNH\text{-}C_6H_4$-*p*	Benzoyl	$C_{22}H_{18}N_4O_2S_2$	232-233	75	Benzene	60.81	4.17	12.92	60.66	4.37	12.92

[a] Solvent of recrystallization was benzene except for **1** which was ethanol.

Table 2

Physical Properties of *N*-Benzoyl-*N'*-quinolylthiourea Derivatives [a]



Compound No.	R	X	Y	Molecular Formula	Mp °C	Yield %	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
31	CH_3	H	H	$C_{18}H_{15}N_3SO$	177-178	65	67.28	4.70	13.08	67.06	4.57	12.98
32	CH_3	Br	H	$C_{18}H_{14}BrN_3OS$	163-165	71	54.00	3.50	10.49	53.91	3.42	10.33
33	CH_3	Br	Br	$C_{18}H_{13}Br_2N_3OS$	252-255	62	45.11	2.73	8.76	45.01	2.55	8.62
34	*p*-C_6H_5Cl	H	H	$C_{23}H_{16}ClN_3OS$	186-188	76	66.10	3.86	10.05	65.97	3.62	10.12
35	*p*-C_6H_5F	H	H	$C_{23}H_{16}FN_3OS$	193-195	72	68.81	4.02	10.46	68.82	3.77	10.37
36	*p*-C_6H_5F	Br	Br	$C_{23}H_{14}Br_2FN_3OS$	275-276	77	49.39	2.52	7.51	49.26	2.41	7.44

[a] The reaction medium was benzene and the solvent of crystallization was ethanol.

Table 3

Characteristic UV, IR and NMR Spectral Data of Phenyl and Pyridyl Substituted Thiourea Derivatives

Compound No.	UV (nm) λ max (log ε)	IR (cm^{-1}) NH	C=O	C=S	R or Ar-H	NH	NMR (δ ppm, J = Hz) H-2	H-3	H-4	H-5	H-6	J_{23}	J_{35}	J_{34}	J_{45}
1	266 (3.54)	3226	—	1143	8.85	8.24 m	7.75	7.14	7.67	6.87	—	5.5	1.8	7.8	8.0
	302 (3.62)				11.18	6.99 m									
2	265 (4.26)	3226	—	1176	9.74	7.64 m	8.20 dd	7.28 m	7.45 m	6.97 d	—	5.2	—	5.6	6.7
	301 (4.31)				13.74										
3	275 (4.43)	3390	1681	1163	8.84	7.77 m	—	8.95 d	7.36 d	—	—	—	—	8.5	—
	323 (4.06)				11.05										
4	268 (4.52)	3226	1667	1149	9.08	7.72 m	8.37 m	—	8.85 dd	7.78 d	—	—	—	—	9.4
	317 (4.29)				13.14										
5	265 (4.32)	3226	1667	1149	9.12	7.70 m	8.81 d	7.25 m	7.71 m	8.43 m	—	7.5	—	8.5	4.6
	312 (4.10)				13.10										
6	260 (4.39)	3226	1667	1149	9.29	7.73 m	8.49 dd	7.35 m	8.32 dd	—	8.75 d	4.9	—	8.3	—
	307 (3.97)				12.68										
7	267 (4.25)	3175	—	1176	8.66	2.33 s	8.09 m	6.85 m	—	6.67 m	—	5.6	—	—	—
	301 (4.37)				8.87										
8	267 (4.32)	3333	—	1163	8.96	2.49 s	—	6.7 dd	7.68 dd	7.37 d	—	—	—	8.0	7.7
	306 (4.46)				9.25	7.29 m									
9	264 (4.29)	3226	1667	1149	9.05	2.41 s	8.28 d	6.98 dd	—	7.26 d	—	4.9	—	—	—
	316 (4.04)				13.05	7.70 m									
10	264 (4.30)	3333	1695	1176	9.04	2.51 s	—	7.00 dd	8.57 d	7.88 d	—	—	1.9	7.8	—
	318 (4.11)				12.94	7.71 m									
11	267 (4.32)	3205	1667	1146	9.20	3.94 s	—	8.00 d	6.78 dd	—	8.28 d	—	—	8.8	—
	325 (3.70)				12.33	7.70 m									
12	263 (4.31)	3279	1667	1149	9.03	7.74 m	—	7.21 dd	8.71 d	7.21 dd	—	—	1.5	7.8	—
	327 (4.15)				12.90										
13	276 (4.46)	3175	—	1235	8.07	7.36 m	—	—	—	—	—	—	—	—	—
14	276 (4.36)	3279	1681	1156	9.11	7.73 m	7.24 s	—	—	8.80 s	—	—	—	—	—
	321 (4.03)				12.82										
15	270 (4.28)	3279	1667	1149	9.13	7.64 m	—	8.43 dd	7.21 m	7.41 m	7.93 dd	—	2.5	8.2	7.5
	316 (3.90)				12.72										
16	267 (4.31)	3279	1667	1147	9.16	7.72 m	7.88 d	—	7.69 dd	7.29 dd	7.45 dd	—	—	—	7.8
	314 (3.90)				12.66										
17	270 (4.28)	3226	1681	1149	10.32	7.81 m	7.45 dd	7.84 dd	—	—	—	—	—	—	—
	318 (3.86)				12.83										
18	255 (4.44)	3226	1695	1163	9.20	7.76 m	—	8.38 dd	8.0 m	8.11 m	7.90 dd	—	1.5	7.9	8.1
	360 (3.48)				13.10										
19	264 (4.50)	3279	1681	1156	9.20	7.64 m	8.32 d	—	8.00 dd	7.81 dd	7.90 dd	—	—	—	8.2
	313 (4.04)				12.85										
20	284 (3.65)	3247	1667	1163	9.21	7.64 m	8.06 dd	8.28 dd	—	—	—	—	—	—	—
	346 (3.41)				11.17										
21	265 (4.44)	3175	1667	1143	9.11	7.70 m	—	—	—	—	—	—	—	—	—
	306 (4.06)				12.57	7.33 s									

Table 3 continued

Compound No.	UV (nm) λ max (log ε)	IR (cm⁻¹) NH	C=O	C=S	R or Ar-H	NMR (δ ppm, J = Hz) NH	H-2	H-3	H-4	H-5	H-6	J_{23}	J_{35}	J_{34}	J_{45}
22	286 (3.61)	3333	1667	1143	9.21	4.08 s	—	7.96 d	—	9.26 dd	7.86 d	—	—	—	—
	370 (3.47)				13.30	7.75 m									
23	241 (4.26)	3226	1667	1149	9.02	3.95 s	—	8.74 dd	7.02 dd	7.18 m	7.91 d	—	—	7.8	7.4
	271 (4.30)				12.84	7.73 m									
	326 (4.02)														
24	276 (4.36)	3333	1681	1149	10.07	2.05 s	7.98 dd	7.49 dd	—	—	—	—	—	—	—
	328 (3.89)				13.50	3.32 [a]									
25	279 (4.34)	3279	1667	1147	9.05	4.04 q	7.88 dd	6.93 dd	—	—	—	—	—	7.9	—
	324 (3.84)				12.57	1.41 t									
						7.58 m									
26	241 (4.29)	3175	1653	1124	9.05	3.87 d	7.08 d	—	—	—	—	—	—	—	—
	277 (4.26)				12.61	7.72 m									
	328 (3.86)														
27	285 (4.35)	3205	1667	1143	9.1	1.16 t	7.43 dd	6.66 dd	—	—	—	—	—	—	—
	390 (3.79)				12.28	3.36 q									
						7.72 m									
28	296 (4.26)	3226	1667	1149	9.17	7.56 m	7.64 dd	7.95 dd	—	—	—	—	—	8.3	—
	356 (4.33)				12.88	7.99 s									
29	252 (4.60)	3226	1667	1163	9.19	7.74 m	—	7.38 dd	—	—	—	—	1.5	6.4	5.9
	320 (4.04)				12.31										
30	276 (4.44)	3311	1667	1147	11.47	7.75 m	—	—	—	—	—	—	—	—	—
	338 (3.93)				12.64	8.00 d									

[a] This band is due to the protons of the NH group in acetamide. The nmr solvent for compounds **1-12** was deuteriochloroform and for **13-30** was deuteriodichloromethane.

Table 4

Characteristic UV, IR and NMR Spectral Data of Quinolyl Substituted Thiourea Derivatives

Compound No.	UV (nm) λ max (log ε)	IR (cm⁻¹) NH	C=O	C=S	R or Ar-H	NMR (δ ppm, J = Hz) in DMSO-d_6 NH	H-2	H-3	H-4	H-5	H-6	J_{56}	J_{57}	J_{78}
31	225 (4.25)	3571	1667	1163	2.68 s		8.22 s	8.06 dd	7.70 m	7.97 m	7.81 dd	8.3	—	8.0
	288 (4.25)				7.62 m									
	334 (4.13)													
32	237 (4.56)	3333	1724	1149	2.72 s		8.18 s	8.07 d	—	7.92 dd	7.85 dd	—	2.0	7.30
	290 (4.05)				7.62 m									
	332 (3.98)													
33	241 (4.75)	3333	1667	1190	2.81 s		8.11 s	7.95 d	—	8.12 d	—	—	2.0	—
	292 (3.91)				7.65 m									
	334 (3.79)													
34	255(4.64)	3333	1639	1163	7.64 m		7.88 s	8.31 dd	7.88 dd	8.04 m	8.18 dd	7.10	—	7.40
	330 (3.98)				8.14 m									
35	267 (4.77)	3226	1724	1156	7.42 m		8.50 s	8.41 dd	8.15 m	8.23 m	7.79 dd	8.10	—	8.5
	329 (4.24)				7.86 m									
36	277 (4.67)	3333	1653	1149	7.59 m		8.32 s	8.10 d	—	—	—	—	2.10	—
	340 (4.04)				7.67 m									
	353 (3.99)													

Abbreviations: s = singlet, m = multiplet, d = doublet, dd = double doublet.

for these compounds [7-9]. Recently, chemical structure and antiviral activity of *N,N'*-diphenylthioureas were studied by synthesis and testing of model compounds. The analysis revealed a number of structural features that are essential for antiviral activity [10].

These findings prompted the preparation of three series of new disubstituted thioureas for biological activity testing, by the reaction of phenyl-, *p*-fluorophenyl- and benzoylisothiocyanates with various substituted anilines, aminopyridines and 4-aminoquinolines. The structure and physical properties of these compounds are given in Tables 1 and 2. The uv, ir and nmr spectral data are pre-

sented in Tables 3 and 4. Because of the difference between oxygen and sulfur in electronegativity, the non-bonded electrons on sulfur are more loosely bound and require less excitation energy. This makes the n → π^* transition of the n-electrons in the C=S bond to appear at longer wavelengths than in its oxygen analogue [11-14]. These compounds exhibited bands in the region 301-353 nm (log ϵ = 3.62-4.46). This band appears in the region 301-320 nm (log ϵ = 3.62-4.59) in the benzene and pyridine derivatives, while the thiourea derivatives containing the quinoline ring systems exhibited absorption at the 321-334 nm region (log ϵ = 3.79-4.04), except in compound **36** where this band appeared at 353 nm (log ϵ 3.99). This band may be an electron-transfer band.

The ir spectra of the disubstituted thiourea derivatives prepared exhibited a C=S stretching vibration in the region between 1190 and 1143 cm^{-1} except in compound **13** where this band appeared at 1235 cm^{-1}. Earlier studies on thiourea derivatives showed the presence of three bands in the region 1570-940 cm^{-1} [16-18]. In addition to the above bands, two other bands appeared in the region 1400-1050 cm^{-1}, one of them is attributed to C-N stretching vibration (amide 111 band) near 1300 cm^{-1} [19-21]. The extreme variations in the assignments of the C=S stretching frequency in thiourea derivatives is undoubtedly due to vibrational coupling effects. In most of these systems, the vibrations due to C-N stretching, C=S stretching and NH bending can interact to give the observed infrared frequencies [21]. The NH absorption bands appeared in the 3390-3226 cm^{-1} region. Khurana, *et al* [14] gave the range 3180-3085 cm^{-1} for the NH absorption in thiourea derivatives containing a quinoline ring system. Benzoyl thiourea derivatives exhibited a C=O stretching vibration in the 1695-1639 cm^{-1} region. The presence of C=O and amide NH groups results in the lowering of the NH absorption frequency. This is due to interaction and hydrogen bonding between these groups [22]. As far as the thiol-thione tautomerism is concerned, we could not observe the SH stretching band in the 2600-2550 cm^{-1} region in accordance with the results of Rao [21].

The nmr spectra of these compounds exhibited two broad absorption bands in the low-field region. These bands were assigned to the NH protons in the NHC=O and NH-C=S groups. The thiol-thione tautomerism is observed in the nmr spectra of these compounds, where a singlet absorption peak appeared in the high field region near 1.2-1.6 ppm, whereas in compounds **4** and **5** this band appeared at 2.14 ppm. This was confirmed by deuteration, where the two NH and the SH absorptions disappeared.

EXPERIMENTAL

Melting points were determined on a Kofler Hot Bench and are uncorrected. Elemental analyses were performed by Alfred Bernhardt Laboratories, Ruhr, Germany. The uv absorption spectra were measured as solutions in ethanol with a Unicam SP 800B uv spectrophotometer. The ir absorption spectra were recorded on a Perkin Elmer 375 spectrophotometer as potassium bromide wafers. The nmr spectra were measured on a Varian HA 100 MHz spectrometer in DMSO-d_6, deuteriodichloromethane or deuteriochloroform with tetramethylsilane (TMS) as internal reference.

Materials.

Phenyl isothiocyanate and 4-fluorophenyl isothiocyanates were Fluka products. Benzoyl isothiocyanate was prepared according to the method of Ampelang [24]. Derivatives of aniline and aminopyridines were available commercially, while 4-aminoquinoline derivatives were prepared from the corresponding amides and will be published later.

General Procedure for the Preparation of Disubstituted Ureas.

To a solution of the amine (0.05 mole) in a suitable solvent (20 ml) (see Tables 1 and 2) was added the isothiocyanate (0.055 mole) dissolved in the same solvent (10 ml). The reaction mixture was left for 0.5 hour at room temperature, when the thiourea derivative was obtained. It was filtered, washed with petroleum ether (bp 40-60°) to remove excess isothiocyanate. Recrystallization of the product from a suitable solvent afforded the pure thiourea derivative. The physical properties of these compounds are given in Tables 1 and 2. The uv, ir and nmr spectral data are given in Tables 3 and 4.

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