Synthesis and Spectral Characterization of Some New *N*-Substituted 2-Aminobenzothiazoles, 2-Aminothiazolopyridines and 2-Aminothiazoloquinolines

George Y. Sarkis* and Essam D. Faisal

Department of Chemistry, College of Science, University of Baghdad,
Baghdad, Jaderiya, Iraq

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A series of *N*-substituted 2-aminobenzothiazoles, 2-aminothiazolopyridines, and 2-aminothiazoloquinolines were prepared by the cyclization of *N,N'*-disubstituted thiourea derivatives by bromine in acetic acid. The uv, ir and nmr data for these compounds are presented and discussed.

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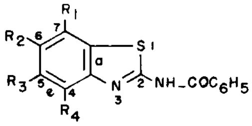
It is well known that substituted 2-aminobenzothiazoles show marked activity in many biological systems. It is found that compounds containing this ring system have antimalarial activity due to the structural similarities to 4-aminoquinoline [1-3]. 2-Alkyl or 2-arylaminobenzothiazoles showed antitubercular activity [4]. Various other thiazole derivatives showed herbicidal [5], anti-inflammatory [6,7], antimicrobial [8] or antiparasitic activity [9]. It was therefore, thought worthwhile to prepare a series of *N*-substituted thiazoles condensed with benzene, pyridine and quinoline ring systems and to study their biological activity and spectroscopic properties. Twenty-seven condensed thiazole derivatives were synthesized by the cyclization of *N,N'*-disubstituted thiourea derivatives [10] by bromine in acetic acid. The structure and physical properties of these compounds are given in Tables 1, 2 and 3. The uv, ir and nmr spectral data are presented in Table 4.

In this work, we have applied the Hugerschoff synthesis [11,12] which was used originally to synthesize benzothiazoles and furothiazoles, to pyridine and quinoline ring systems to obtain thiazolopyridines and thiazoloquinoline. When *N*-benzoyl *N'*-3(2,6-dichloropyridyl)thiourea was cyclized with bromine in acetic acid, it was expected that sulphur will attack position-4 of the pyridine ring, but actually the attack was at position-2 of the ring with displacement of the chlorine atom to give thiazole **24**.

The uv absorption spectra of these compounds showed a bathochromic shift when compared with the parent 2-aminobenzothiazole [12,13], and simple thiazoles and bithiazoles [15,16]. On going to *N*-substituted-2-aminothiazolopyridines, and compare absorption maximum of **15** and **22**, we find that **15** shows maximum absorption at 242 nm ($\log \epsilon = < 4.415$), and 314 nm ($\log \epsilon = 4.249$). While in **22** maximum absorption occurs at 312 nm ($\log \epsilon = 4.327$),

Table 1

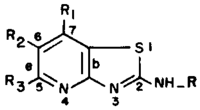
Physical Properties of 2-Benzamidobenzothiazole Derivatives



Compound No	R_1	R_2	R_3	R_4	Molecular Formula	Mp °C	Yield %	Solvent of crystallization	Analyses % Calcd. C	H	N	Found C	H	N
1	H	Cl	H	H	$C_{14}H_9ClN_2OS$	234-235	57	Methanol	58.23	3.14	9.70	58.31	3.20	9.81
2	H	H	H	Cl	$C_{14}H_9ClN_2OS$	252-253	42	EtOH/EtAc	58.23	3.14	9.70	58.30	3.21	9.91
3	NO_2	H	H	H	$C_{14}H_9N_3O_3S$	225-226	35	Ethanol	56.18	3.03	14.03	56.22	3.16	14.16
4	H	H	NO_2	H	$C_{14}H_9N_3O_3S$	239-240	44	Ethyl acetate	56.18	3.03	14.03	56.31	3.25	14.21
5	H	NO_2	H	H	$C_{14}H_9N_3O_3S$	255-256	75	EtOH/EtAc	56.18	3.03	14.03	56.22	3.15	14.11
6	H	H	H	NO_2	$C_{14}H_9N_3O_3S$	240-242	70	Ethanol	56.18	3.03	14.03	56.26	3.10	14.01
7	H	$NHCOCH_3$	H	H	$C_{16}H_{13}N_3O_2S$	234-235	86	Methanol	61.72	4.21	13.49	61.55	4.31	13.52
8	OCH_3	OCH_3	OCH_3	H	$C_{17}H_{16}N_2O_4S$	222-223	80	Ethanol	59.29	4.68	8.31	59.09	4.61	8.01
9	H	$N(C_2H_5)_2$	H	H	$C_{13}H_{19}N_3OS$	239-240	90	Ethanol	66.43	5.88	12.91	66.35	5.80	12.85
10	H	$N=NC_6H_5$	H	H	$C_{20}H_{14}N_4OS$	242-243	97	$CHCl_3$/EtOH	67.02	3.93	15.63	67.15	4.01	15.70
11	—	— 2-Benzamidothiazolo[5,4-*e*]			$C_{22}H_{14}N_4O_2S_2$	213-214	52	EtOH/EtAc	61.38	3.27	13.01	61.26	3.21	13.11

Table 2

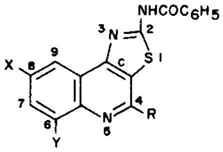
Physical Properties of *N*-Substituted 2-Aminothiazolo[4,5-*b*]pyridines



Compound No	R_1	R_2	R_3	R	Molecular Formula	Mp °C	Yield %	Solvent of crystallization	Analyses % Calcd. C	H	N	Found C	H	N
12	H	H	H	*p*-FC_6H_5-	$C_{12}H_8FN_3S$	277-278	95	Ethanol	58.76	3.28	17.13	58.83	3.48	17.21
13	H	H	H	-C_6H_5-	$C_{12}H_9N_3S$	226-227	81	Ethanol	63.41	3.99	18.48	63.46	3.92	18.16
14	H	Cl	H	-COC_6H_5	$C_{13}H_8ClOS$	258-259	95	Ethanol	53.89	2.78	14.50	53.80	2.72	14.52
15	H	H	H	-COC_6H_5	$C_{13}H_9N_3OS$	255-256	92	Ethanol	61.13	3.49	16.47	61.16	3.55	16.46
16	CH_3	H	H	-C_6H_5	$C_{13}H_{11}N_3S$	228-230	83	Ethanol	64.65	4.59	17.40	64.78	4.67	17.20
17	H	H	CH_3	-C_6H_5	$C_{13}H_{11}N_3S$	308-310	91	Methanol	64.65	4.59	17.40	64.60	4.62	17.38
18	CH_3	H	H	-COC_6H_5	$C_{14}H_{11}N_3OS$	234-235	90	Ethanol	62.43	4.11	15.60	62.31	4.01	15.63
19	H	H	CH_3	-COC_6H_5	$C_{14}H_{11}N_3OS$	233-234	45	EtOH/EtAc	62.43	4.11	15.60	62.40	4.08	15.55
20	2-Benzamidothiazolo[4,5-*d*]			-COC_6H_5	$C_{21}H_{13}N_5O_2S_2$	185-186	92	Ethanol	58.45	3.03	16.23	58.37	3.17	16.08
21	H	H	Cl	-COC_6H_5	$C_{13}H_8ClN_3OS$	228-230	93	Ethanol	53.89	2.78	14.50	53.87	2.72	14.55

Table 3

Physical Properties of 2-Benzamidobenzothiazolo[5,4-*c*]quinolines [a]



Compound No.	X	Y	R	Molecular Formula	Mp °C	Yield %	Analyses % Calcd. C	H	N	Found C	H	N
22	H	H	CH_3	$C_{18}H_{13}N_3OS$	317-318	92	67.69	4.10	13.15	67.54	4.15	13.09
23	Br	H	CH_3	$C_{18}H_{12}BrN_3OS$	279-280	80	54.28	3.03	10.55	54.12	2.98	10.21
24	Br	Br	CH_3	$C_{18}H_{11}Br_2N_3OS$	350-351	70	45.30	2.32	8.80	45.25	2.33	8.75
25	H	H	-C_6H_4Cl (*p*)	$C_{23}H_{14}ClFN_3OS$	279-280	77	66.42	3.39	10.10	66.33	3.26	10.03
26	H	H	-C_6H_4F (*p*)	$C_{23}H_{14}N_3FOS$	238-240	85	69.15	3.53	10.51	69.02	3.45	10.71
27	Br	Br	-C_6H_4F (*p*)	$C_{23}H_{12}Br_2FN_3OS$	289-290	72	48.15	2.10	7.32	48.02	2.07	7.23

[a] Solvent of recrystallization is ethanol, except for **24**, which is ethyl acetate.

and 352 nm (log ϵ = 3.242). This indicates that when the two nitrogen atoms are far apart in the conjugated system, there is a better transmission of conjugation from the chlorine atom to the NHR group. While in **15**, where the two nitrogen atoms are closer together, the electron density is concentrated in this region, thereby weakening the transmission of conjugation.

The ir absorption data for the thiazoles synthesized are presented in Table 4. When comparing the ir data of these compounds with the corresponding thiourea derivatives, it was found that the NH stretching absorption appeared at high frequency near 3333 cm^{-1}. On the other hand, the carbonyl stretching vibration appeared at a lower frequency than in thiourea derivatives [10]. This variation of the position and intensity of the C=O and NH bands is attributed to the intermolecular and intramolecular hydrogen bonding between the C=O and NH groups [18,19].

The chemical shifts and coupling constants in the nmr spectra of the compounds synthesized are summarized in Table 4.

The nmr spectrum of compound **22** shows that the sulfur atom attacks position 2 of the pyridine ring with elimination of the chlorine atom and not position 4 to give *N*-substituted 2-aminothiazolo[5,4-*b*]pyridine and not *N*-substituted 2-aminothiazolo[5,4-*c*]pyridine. The spectrum shows two double doublets, one for H-3 at 8.38 ppm, while H-4 absorbed at 7.36 ppm (J_{34} = 7.8 Hz). When the intermediate *N*-(3-nitrophenyl)-*N'*-benzoylthiourea was cyclized by bromine in acetic acid, two thiazoles **3** and **4** were obtained which were separated by fractional crystallization and identified by their nmr spectra. Compound **3** showed three double doublets at 7.40, 8.03 and 8.52 ppm, each integrating for one proton. While compounds **4** showed again three double doublets at 7.93, 8.05 and 8.64 ppm. All the protons in **4** are deshielded as they are adjacent to the nitro group.

Table 4

UV, IR and NMR Spectral Data for *N*-Substituted 2-Aminobenzothiazoles, 2-Aminothiazolopyridines and 2-Aminothiazoloquinolines

Compound No.	UV (nm) λ max (log ε)	IR (cm^{-1}) NH	C=O	C=C, C=N	NMR (ppm) J (Hz) R or Ar-H	H-4	H-5	H-6	H-7
1	238 (4.32), 264 (4.25), 306 (4.31)	3279	1695	1613, 1563, 1493	7.57 m ($J_{12} = 8.4$, $J_{24} = 2$)	7.36 d	8.01 dd	—	7.65 d
2	275 (4.14), 306 (4.31)	3226	1613	1613, 1600, 1527	7.50 m ($J_{23} = 7.3$, $J_{24} = 1.9$, $J_{34} = 7.7$)	—	7.60 dd	7.3 dd	7.26 dd
3	275 (3.91)	3333	1695	1639, 1600, 1515	7.7 m ($J_{12} = 8.8$, $J_{23} = 9.3$)	8.03 dd	7.4 dd	8.5 dd	—
4	252 (4.32), 329 (3.35)	3247	1695	1600, 1563, 1515	7.61 m ($J_{13} = 2$, $J_{14} = 1.4$, $J_{34} = 8.8$)	8.64 d	—	8.05 dd	7.93 dd
5	235 (4.12), 315 (4.15)	3289	1695	1600, 1550, 1527	7.59 m ($J_{12} = 9.3$, $J_{24} = 2$)	7.84 d	8.22 dd	—	7.99 d
6	245 (4.22), 340 (3.30)	3226	1695	1575, 1493	7.76 m ($J_{23} = 8.8$)	—	8.46 dd	8.02 dd	8.14 dd
7	283 (4.26), 354 (3.62)	3279	1709 1672	1575, 1515, 1471	2.02 s 7.53 m	8.0 d	7.24 dd ($J_{12} = 7.9$, $J_{24} = 2$)	—	7.38 d
8	230 (4.11), 267 (4.21) 307 (4.25)	3333	1680	1613, 1527, 1471	3.81 d 3.90 d 4.03 d 7.86 m	7.16 s	—	—	—
9	—	3448	1709	1613, 1587, 1515	2.51 q 1.64 t 7.75 m	7.86	7.63 dd ($J_{12} = 6.9$, $J_{24} = 1.9$)	—	7.24 d
10	338 (3.83), 354 (3.94)	3226	1709	1613, 1558, 1504	7.53 m 7.88 s	7.6 d	8.04 dd ($J_{12} = 8.8$)	—	7.83 d
11	234 (4.49), 283 (4.16)	3226	1695	1587, 1515, 1449	7.85 m	—	— ($J_{34} = 7.8$)	7.48 d	7.48 d
12	259 (4.15), 347 (3.72)	3333	—	1613, 1587, 1460	9.81 d 7.71 d	— ($J_{AB} = 7.34$, $J_{23} = 5.6$, $J_{34} = 5.9$)	8.75 dd	7.99 dd	8.27 dd
13	234 (4.31), 278 (4.31) 318 (4.34)	3333	—	1600, 1538, 1515	7.25 s —	— ($J_{23} = 6.7$, $J_{24} = 1.5$, $J_{34} = 7.9$)	8.43 dd	7.46 dd	7.91 dd
14	242 (4.41), 264 (4.25), 314 (4.15), 348 (4.25)	3333	1613	1515, 1449	7.90 m	—	8.07 d ($J_{24} = 1.9$)	—	9.29 d
15	242 (4.31), 305 (4.12), 339 (4.27)	3333	1639	1538, 1493, 1493, 1449	7.92 m	— ($J_{23} = 6.4$, $J_{24} = 1.5$, $J_{34} = 6.85$)	8.99 dd	7.39 dd	8.02 dd
16	276 (4.10), 317 (4.20), 347 (3.39)	3333	—	1653, 1587, 1527	2.58 s 7.70 s	—	8.86 d ($J_{23} = 6.2$)	7.69 d	—
17	276 (4.11), 321 (4.21), 349 (3.44)	3279	—	1613, 1587, 1439	2.54 s	—	— ($J_{34} = 6.7$)	—	7.91 d
18	243 (4.42), 303 (4.14), 336 (4.36)	3333	1645	1538, 1493, 1449	2.49 s 7.90 m	—	8.84 d ($J_{23} = 6.8$)	7.21 d	—
19	240 (4.32), 307 (4.12), 342 (4.31)	3448	1626	1587, 1527, 1493	2.82 s 7.76 m	—	— ($J_{34} = 7.2$)	7.25 d	8.25 d
20	245 (4.49), 315 (4.27)	3333	1681	1587, 1449	7.60 m	—	—	—	8.04 s
21	312 (4.32), 352 (3.24)	3390	1667	1575, 1538	7.70 m	—	— ($J_{34} = 7.8$)	8.38 d	7.36 d
						H-9	H-8	H-7	H-6
22	232 (4.47), 321 (4.0), 321 (4.00) 336 (3.89)	3333	1667	1587, 1550, 1515, 1493	3.07 s 7.67 m	8.6 dd	7.69 m ($J_{57} = 2.1$, $J_{56} = J_{78} = 8.3$)	8.21 m	7.95 dd

Table 4, continued

Compound No.		IR (cm^{-1})			NMR (ppm) J (Hz)				
	λ max (log ε)	NH	C=O	C=C, C=N	R or Ar-H	H-4	H-5	H-6	H-7
23	257 (4.51), 322 (3.86)	3279	1667	1600, 1575, 1493	2.78 s 7.94 m	8.80 d (J_{57} = 2.0, J_{78} = 7.1)	—	8.11 dd	8.03 dd
24	241 (4.66), 293 (3.90), 336 (3.77)	3333	1667	1613, 1587, 1493	2.92 s 7.85 m	8.35 d	—	8.44 d	—
25	255 (4.55), 320 (3.97)	3226	1626	1587, 1563, 1481	7.71 m 8.32 m	8.96 dd (J_{56} = J_{78} = 7.6)	7.78 m	7.80 m	8.02 dd
26	267 (4.52), 312 (4.26)	3333	1667	1613, 1563, 1493	7.36 m 7.75 m	8.33 dd (J_{56} = J_{78} = 8.2)	7.96 m	8.04 m	7.62 dd
27	229 (4.46), 240 (4.0), 277 (4.65), 353 (3.96)	3279	1639	1600, 1563, 1504, 1471	7.32 m 7.40 m	8.33 d (J_{57} = 2.2)	—	8.51 d	—

Abbreviations: a = singlet, d = doublet, dd = double doublet.

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 with tetramethylsilane (TMS) as the internal reference.

General Procedure for the Preparation of Condensed Thiazole Derivatives.

A suspension of the *N,N'*-disubstituted thiourea derivaive [10] (0.2 mole) in acetic acid (10-20 ml) was heated gently to give a clear solution (60°). Bromine (0.21 mole) in acetic acid (2 ml) was then added dropwise to the stirred solution and after addition was complete, the mixture was left at ambient temperature for 1 hour. The precipitated substance was then collected, triturated with acetic acid and ether and recrystallized from a suitable solvent. The physical properties of the synthesized compounds are given in Tables 1, 2 and 3.

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