2-AMINO-SUBSTITUTED DERIVATIVES OF BENZIMIDAZOLES FROM 2-ISOTHIOCYANATO CARBOXYLATES

Ľubomír FLOCH[a], Michal UHER[a] and Ján LEŠKO[b]

[a] *Department of Organic Chemistry, Slovak Technical University, 812 37 Bratislava and*
[b] *Laboratory of Mass Spectrometry, Slovak Technical University, 812 37 Bratislava*

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2-Isothiocyanato carboxylates react with *o*-phenylenediamine to give N,N′-substituted thioureas, which cyclize to yield 2-amino-substituted derivatives of imidazole. The structure of these compounds was corroborated by IR, UV, ^{1}H, ^{13}C NMR, and mass spectral methods.

Recently, we reported on the synthesis of benzimidazole derivatives from carbonyl isothiocyanates[1] and on cyclization of glycosyl isothiocyanate[2] and aromatic isothiocyanates[3] with *o*-phenylenediamine. This paper concerns the synthesis of heterocyclic compounds from 2-isothiocyanato carboxylates and their reaction with *o*-phenylenediamine.

The starting esters of 2-isothiocyanato carboxylic acids obtained by the thiophosgene method[4] were reacted with *o*-phenylenediamine in benzene. The reaction course was monitored by thin-layer chromatography (Table I). The resulting substituted thioureas were cyclized to benzimidazoles either with dicyclohexylcarbodiimide (DCC) or with the red modification of mercury oxide. A corresponding carbodiimide presuming to be the intermediate[3] underwent a nucleophilic reaction with the free amino group of *o*-phenylenediamine (Table II, derivatives *IIa*–*IIe*). To verify the proposed mechanism, N-(2-methylaminophenyl)-N′-(1-carbethoxymethyl)thiourea (*If*) and N-methyl-N-(2-aminophenyl)-N′-carbethoxymethyl)thiourea (*Ig*) were synthesized; compound *If* afforded 1-methyl-2-amino-substituted benzimidazole, whilst *Ig* did not react (Scheme 1). N-Phenyl-N′-carbethoxymethylthiourea (*Ih*) furnished with the red modification of mercury oxide the corresponding carbodiimide, as evidenced by IR spectra (N=C=N, 2 120 cm^{-1}).

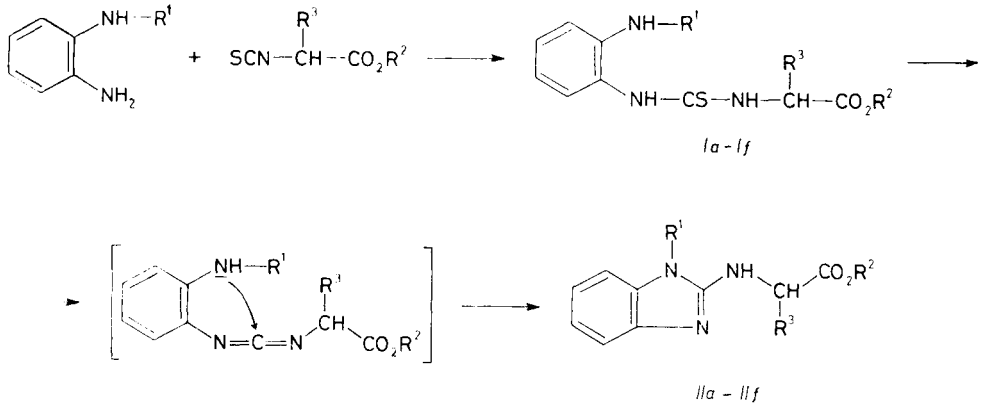
The ν(N—H) bands of thioureas *Ia*–*Ig* appeared at 3 255 to 3 492 cm^{-1}, the ν(CO) absorption at 1 732 to 1 744 cm^{-1}. The conversion of isothiocyanate group into thiourea was associated with a change of the originally split ν(CO) band of the carbethoxy grouping[5] into a sharp simple absorption; consequently, the wave number was shifted by 14–18 cm^{-1} towards lower values. The ν(CO) wave numbers of carbethoxyl or carbmethoxyl groups of 2-amino-substituted benzimidazoles

TABLE I

Physicochemical properties of substituted thioureas *I*

Compound	Formula M.w.	M.p., °C Yield, %	Calculated/Found			Mass spectra, *m/z* rel. int., (%)
			% C	% H	% N	
Ia	$C_{11}H_{15}N_3O_2S$ 253·2	96—99 69	52·19 52·45	5·96 5·66	16·58 16·70	253 (50), 220 (57), 207 (64), 174 (71), 150 (5), 146 (100), 118 (28), 108 (60), 74 (35), 65 (28), 59 (78)
Ib	$C_{14}H_{21}N_3O_2S$ 295·4	151—153 60	56·92 56·71	7·16 6·99	14·22 14·01	295 (22), 262 (55), 249 (31), 216 (34), 188 (100), 149 (38), 134 (31), 119 (14), 118 (17), 108 (43), 92 (16), 91 (8)
Ic	$C_{15}H_{23}N_3O_2S$ 309·4	101—104 91	58·23 58·40	7·49 7·69	13·58 13·40	309 (17), 276 (32), 263 (43), 230 (65), 202 (100), 160 (19), 150 (35), 149 (14), 146 (17), 118 (17), 108 (29), 91 (8)
Id	$C_{18}H_{21}N_3O_2S$ 343·4	116—118 73	62·95 62·69	6·16 6·16	12·24 12·04	343 (7), 297 (70), 264 (74), 236 (100), 151 (17), 150 (22), 134 (18), 120 (26), 119 (26), 118 (26), 108 (15), 103 (13), 91 (70)
Ie	$C_{13}H_{17}N_3O_4S$ 311·3	193—196 75	50·14 50·18	5·50 5·79	13·49 13·79	—
If	$C_{12}H_{17}N_3O_2S$ 267·3	81—83 24	53·91 53·68	6·41 6·40	15·72 15·55	—

IIa–IIf were lower than those of thioureas *Ia–If*; their values are comparable with the wave numbers of substituted acetic acids[6].



Ia–If

IIa–IIf

In formulae *I* and *II*: *a*, $R^1 = H$; $R^2 = C_2H_5$; $R^3 = H$ *b*, $R^1 = H$; $R^2 = C_2H_5$; $R^3 = CH(CH_3)_2$ *c*, $R^1 = H$; $R^2 = C_2H_5$; $R^3 = CH_2CH(CH_3)_2$ *d*, $R^1 = H$; $R^2 = C_2H_5$; $R^3 = CH_2C_6H_5$ *e*, $R^1 = H$; $R^2 = CH_3$; $R^3 = CH_2CO_2CH_3$ *f*, $R^1 = CH_3$; $R^2 = C_2H_5$; $R^3 = H$

SCHEME 1

The UV spectrum of 2-aminobenzimidazole[7] (244 nm, log ε 3·83; 283 nm, log ε 3·89) is in a good agreement with the λ_{max} and log ε values of benzimidazoles *IIa–IIf* (Table II). The absorption maxima of thioureas *Ia–If* at 243 ± 1 nm (log ε 4·0 to 4·26) are due to $\pi \rightarrow \pi^*$ transitions of the aromatic ring, those at 298–303 nm (log ε 3·14–3·68) to $n \rightarrow \pi^*$ transitions of an HNC=S system.

The ^{1}H NMR spectra backed the structure of thioureas *Ia–If* (Table III). Treatment of the deuteriochloroform solutions of thioureas *Ia–Id*, *If*, and *Ig* with D_2O led to disappearance of all N—H proton signals; accordingly, multiplicities of H-4 protons changed from dd in *Ib* into d ($^3J(4, 1) = 5$ Hz), from m in *Id* to dd ($^3J(4, 1) = 6$ Hz), and from d to s in *Ia*, *If–Ii*. Thus the coupling constants of H-4 with H-1′ at R^3 could be estimated.

The protons of aromatic ring in the spectrum of *IIf* (Table IV) appeared as multiplets of an ABCD system[8]. Due to prototropy at nitrogens of the imidazole skeleton the protons of aromatic ring in compounds *IIa–IIe* afforded a series of two four-spin signals (an AA′BB′ system). The more shielded H-4 and H-7 protons (AA′) have lower chemical shift values when compared with those of H-5 and H-6 (BB′). Interaction between the H-8 and the adjacent N—H protons did not occur, their doublet-doublet structure is associated with interaction with diastereotropic protons at C-1′. The dd multiplicity of H-8 in *IIe* appeared as a triplet. The chemical shift values

TABLE II

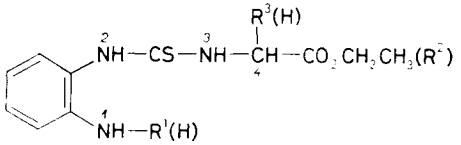
Physicochemical properties of substituted 2-amino benzimidazoles *II*

Compound	Formula M.w.	M.p., °C Method, Yield (%)	Calculated/Found % C	% H	% N	Mass spectra, *m/z* rel. int. (%)	UV spectra[d] λ_{max} nm	log ε $m^2\ mol^{-1}$
IIa	$C_{11}H_{13}N_3O_2$ 219·1	192—194[a] *A*(49), *B*(73)	60·26 60·40	5·97 6·02	19·16 19·38	219 (25), 174 (3), 173 (3), 147 (11), 146 (100), 145 (8), 119 (10), 118 (28) 92 (4), 91 (6), 90 (5)	212·5 245·0	4·37 3·09
IIb	$C_{14}H_{19}N_3O_2$ 261·3	251—254[a] *A*(50), *B*(68)	64·35 64·30	7·33 7·29	16·08 16·19	261 (5), 188 (12), 145 (4), 136 (24) 118 (4), 106 (100), 105 (4), 91 (4), 79 (70)	211·5 247·0 287·0	4·94 4·01 4·07
IIc	$C_{15}H_{21}N_3O_7$ 275·3	159—161[a] *A*(52), *B*(65)	65·43 65·49	7·68 7·79	15·26 15·25	275 (5), 219 (42), 202 (99), 173 (100) 160 (48), 158 (45), 146 (37), 145 (90) 133 (75), 118 (58), 91 (13), 90 (25)	215·0 247·0 287·0	3·64 3·93 4·03
IId	$C_{18}H_{19}N_3O_2$ 309·4	110—112[b] *B*(51)	69·88 69·63	6·19 6·01	13·58 13·42	309 (18), 263 (24), 236 (15), 218 (24) 172 (9), 144 (20), 134 (12), 133 (100), 118 (11), 91 (36)	217·0 234·0 285·0	4·19 3·86 3·97
IIe	$C_{13}H_{19}N_3O_4$ 313·4	162—164[c] *B*(44)	49·82 49·68	6·11 6·05	13·41 13·32			
IIf	$C_{12}H_{15}N_3O_2$ 233·3	130—131 *B*(66)	61·78 61·65	6·48 6·42	18·01 17·97	233 (18), 188 (3), 160 (100) 132 (13), 131 (10), 119 (7), 118 (5), 91 (4) 77 (8)	212·4 205·5 284·4	4·30 3·43 3·56

[a] From acetone–ether (2 : 1); [b] from benzene–petroleum ether (1 : 3); [c] from chloroform–ether (1 : 6); [d] in CH_3OH.

TABLE III

^{1}H NMR chemical shifts (δ, ppm) and coupling constants (J, Hz) of substituted thioureas *I*



Compound	H-Arom.	N(1)-H	N(2)-H	N(3)-H $^3J(3, 4)$	H-4 $^3J(4, 3')$	R^2-protons ^3J		R^3-protons
Ia	7·12—7·62 m	3·18 bs	8·42 bs	—	4·34 d 6	1·25 t 7·5	4·15 q	—
Ib	6·68—7·37 m	4·37 bs	8·25 bs	6·47 d 9·0	5·03 dd 9·5	1·26 t 7·2	4·22 q	0·86 d, 0·97 d 2·22 m, $^3J(1, 2') = 3$
Ic	6·68—7·30 m	3·97 bs	8·10 s	6·25 d 8	5·12 m	1·37 z 7·5	4·20 q	0·88 d, 0·96 d 1·50—1·75 m
Id	6·56—7·29 m	3·83 bs	8·03 s	6·33 d 8	5·31 m 8 (6)[a]	1·22 t 7·0	4·15 q	3·16 m
Ie	6·80—7·20 m	3·28 bs	9·05 s	5·66 bs	4·65 m	3·68 s	—	3·10 m, 3·80 s
If[b]	7·25—7·55 m	2·66 bs	8·95 s	5·92 bs	4·35 d 5	1·23 t 7·2	4·07 q	—
Ig[c]	7·24—7·55 m	3·20 bs	—	5·92 bs	4·33 d 5	1·23 t 7·0	4·10 q	

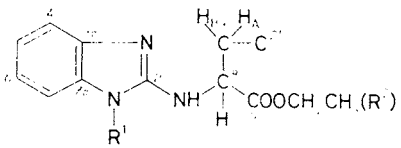
[a] $^3J(4, 1')$; [b] 2·67 s (N(2)-CH_3); [c] 3·67 s (N(2)-CH_3).

of protons at R^1, R^2 and R^3 and the coupling constant values are in line with data published in ref.[9].

The ^{13}C NMR spectra of compounds *IIa*–*IIf* (Table V) are also consistent with the proposed structure. The highest chemical shift values belong to C-2 due to their position between two nitrogen atoms. The chemical shift values for C-4 and C-7, C-5 and C-6, C-3a and C-7a are equal in compounds *IIa*–*IIe* owing to symmetry of the imidazole skeleton caused by a rapid prototropy between N-1 and N-3 nitrogens[10]. Substitution of N-1 by a methyl group suppress prototropy and enables to resolve chemical shifts in agreement with the work by Grundeman and coworkers[11].

TABLE IV

^1H NMR chemical shifts (δ, ppm) and coupling constants (J, Hz) of substituted 2-aminobenzimidazoles *II*

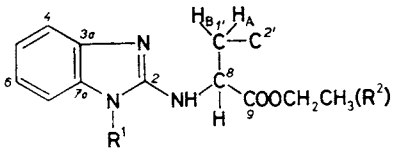


Compound	H-Arom.	H-8 $^3J^a$	R^2-protons ^3J	R^3-protons
IIa[b]	6·89—7·20 m	4·25 s	1·25 t, 4·25 q 7·2	
IIb	6·90—7·27 m	4·31 dd 5·0	1·26 t, 4·15 q 7·0	0·97 d, 1·12 d 2·08 m $CH(CH_3)_2$ $^3J(1', 2') = 6$
IIc	6·98—7·21 m	4·62 dd 5·7	1·20 t, 4·12 q 6·9	0·90 d, 0·92 d 1·59—1·82 m (CH_2) $^3J(2', 3') = {}^3J(2', 4') = 4·2$
IId	6·99—7·22 m	4·91 dd 6·0	1·19 t, 4·12 q 7·0	3·15 dd, 3·27 dd, $^3J(8, 1') = 6·0$, $^2J(1'\,A, 1'\,B) = 13·6$
IIe	7·10—7·35 m	4·51 dd 6·0	3·78 s, 3·81 s	3·12 dd, 3·22 dd $^3J(8, 1'\,A) = 6$, $^3J(1'\,A, 1'\,B) = 16·5$
IIf[c]	7·12—7·51 m	4·30 s	1·28 t, 4·23 q 7·2	

[a] $^3J(8, 1'\,A) = {}^3J(8, 1'\,B)$; [b] in hexadeuteroacetone; [c] 3·33 s (CH_3N), 6·88 bs (NH).

TABLE V

^{13}C NMR chemical shifts (δ, ppm) of substituted 2-aminobenzimidazoles *II*



Compound	C-2	C-3a	C-4	C-5	C-6	C-7	C-7a	C-8	C-9	CH_3	CH_2	R^3-carbons
IIa[a]	156·0	—	112·5	121·0	121·0	112·5	—	45·5	172·5	14·50	61·50	—
IIc[b]	154·14	137·62	112·65	120·73	120·73	112·65	137·62	54·74	174·89	14·04	61·58	41·51 (CH_2), 24·93 (CH) 22·81, 22·00 (2× CH_3)
IId[b]	153·37	136·10	112·53	120·98	120·98	112·53	136·10	56·85	172·87	14·06	61·79	38·13 (CH_2), 136·00, 129·43, 128·51, 127·08 (C-Ph)
IIe[b]	152·51	135·60	125·50	116·47	116·47	125·50	135·60	55·47	170·03	53·30	—	34·58 (CH_2), 168·58 (CO) 52·19 (OCH_3)
IIf[c]	153·80	140·93	116·42	121·22	119·79	107·35	135·02	44·81	171·41	14·16	61·60	—

[a] In hexadeuteroacetone; [b] in $CDCl_3$; [c] 28·08 (NCH_3).

The chemical shift values of carbons in R^3 are in accordance with the ^{13}C NMR data for molecules containing phenylalanine[12], valine[12], leucine[13] or aspartate[14] residues.

The molecular radical ions of *Ia*–*Id* (Table I) eliminate the ·SH radical and ethanol (or reversely), as evidenced by the presence of metastables. Further loss of CO led to formation of base peaks. The main fragmentation pathway of 2-amino-substituted benzimidazoles *IIa*–*IId*, *IIf* (Table III) is represented by the cleavage of a carbethoxy radical to give fragment ions of various intensity (12–100%). The benzimidazole ring of all compounds is diagnosed by ions at *m/z* 91 and 118 with a metastable transition at *m/z* 70·2. The high intensity of the peak at *m/z* 91 of compound *IId* is associated with the occurence of a tropylium ion.

A successive elimination of neutral molecules C_4H_8, C_2H_5OH, CO and HCN from the molecular radical ion of *IIc* (*m/z* 275) afforded fragment ions at *m/z* 219, 173, 145, 118 with corresponding metastables. Cleavage of an ethoxycarbonyl radical from the molecular radical ion gives rise to a very intense fragment ion at *m/z* 202 (99%) and another one at *m/z* 135 (75%) resulting from β-cleavage.

EXPERIMENTAL

(±)-Glycine, valine, leucine, phenylalanine and aspartic acid were commercial products of Lachema (Brno) and Reanal (Budapest), *o*-phenylenediamine (Lachema) was crystallized from benzene prior to use, and 1-methylamino-2-aminobenzene was synthesized according to[15].

The melting points were determined with a Kofler micro hot-stage, the IR spectra of chloroform solutions or KBr pellets, and the UV spectra of methanolic solutions were measured with Specord 71 IR and Specord UV-VIS (Zeiss, Jena) spectrophotometers, respectively. The ^1H NMR spectra of compounds *Ia*–*If* and *IIb* in deuteriochloroform were recorded with a Tesla BS 487 C (80 MHz) apparatus at 25°C. The ^1H and ^{13}C NMR spectra of compounds *IIa* and *IIc*–*IIe* in deuteriochloroform or acetone were run with a UXR 300 (Varian) instrument operating at 300 MHz and 75·43 MHz for ^1H and ^{13}C nuclei, respectively, at 28°C, tetramethylsilane being the internal reference.

The mass spectra were measured with an MS 902 S (AEI, Manchester) spectrometer at an ionization electron energy 70 eV and trap current 100 μA.

Reactions of 2-Isothiocyanato Carboxylates with 1,2-Diaminobenzene or 1-Amino-2-methylaminobenzene

Isothiocyanate (20 mmol) in benzene (20 ml) was added dropwise to a stirred solution of 1,2-diaminobenzene (2·16 g, 20 mmol) or 1-amino-2-methylaminobenzene (2·22 g, 20 mmol) in benzene (60 ml) at 50–60°C, within 15 min. The mixture was stirred for further 2–3 h at room temperature under exclusion of air moisture. The reaction course was monitored by thin-layer chromaography on SiO_2 with $CHCl_3$–EtOH (95 : 5). The mixture was concentrated under reduced pressure to a 2/3 of the original volume to which the same volume of ether or petroleum ether was added. The crude product *Ia*–*Ie* was crystallized from acetone–ether (3 : 1). The reaction with 1-amino-N-methylaminobenzene afforded *If* in 24% yield and the isomeric N-methyl-N-(2-aminophenyl)-2′-(ethoxycarbonylmethyl)thiourea (*Ig*), m.p. 92–94°C in 54% yield. Their ^1H NMR spectral data are listed in Tables III and I, respectively.

N-Phenyl-N′-methoxycarbonylmethyl Thiourea (*Ih*) and
N-Methyl-N-phenyl-N′-ethoxycarbonyl Thiourea (*Ii*)

Methyl isothiocyanatoacetate and aniline in ether gave at an ambient temperature *Ih*, m.p. 78—80°C in 93% yield. ^{1}H NMR spectrum ($CDCl_3$, 80 MHz): 3·71 s, 3 H; 4·40 d, 2 H, ^3J = = 6 Hz; 6·87 t, 1 H, ^3J = 6 Hz; 7·30 s, 5 H; 8·97 s, 1 H.

The isothiocyanatoacetate and N-methylaniline furnished *Ii* in 95% yield, m.p. 59—60°C. ^{1}H NMR spectrum ($CDCl_3$, 80 MHz); 1·23 t; 4·07 q; ^3J = 7 Hz; 3·68 s, 3 H; 4·35 d, 2 H, ^3J = 5 Hz; 5·92 bs, 1 H; 7·25—7·55 m, 5 H. ^{13}C NMR ($CDCl_3$): 14·10 (CH_3); 43·47 (OCH_2); 47·33 (NCH_3); 61·43 (CH_2NH); 126·89, 128·72, 130·58, 142·46 ($C_{arom.}$); 169·89 (C=S); 181·83 (C=O).

Cyclization of Thioureas *IIa—IIf*

A) Dicyclohexylcarbodiimide (0·66 g, 3·2 mmol) in benzene (5 ml) was added to a boiling solution of the respective thiourea (2·5 mmol) in benzene (25 ml) and the solution was refluxed for 3—4 h. The reaction course was monitored by thin-layer chromatography on silica gel with $CHCl_3$–EtOH (92 : 8). Dicyclohexylthiourea separated on standing as a by-product (R_F 0·85), m.p. 172—176°C. The filtrate was concentrated and the separated 2-amino-substituted benzimidazoles *IIa—IIc* were filtered off. Their ^{1}H NMR data are presented in Table III.

B) A red modification of mercury oxide (2,5 mmol) was added to a boiling solution of thiourea (2·5 mmol) in benzene (25 ml). The mixture turned successively dark as a result of precipitation of the black HgS, which was filtered off from the hot mixture and washed with a small amount of hot benzene. Ether was added to the clear filtrate to the first turbidity and the solution was left to crystallize (Table II, derivatives *IIa—IIf*).

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REFERENCES

1. Uher M., Berkeš D., Leško J., Floch Ľ.: Collect. Czech. Chem. Commun. *48*, 1651 (1983).
2. Ogura H., Takanashi H.: Heterocycles *6*, 1633 (1977).
3. Omar A., Monseu M. E., Habib N. S., Aboulwafa O. M.: Synthesis *1977*, 864.
4. Floch Ľ., Kováč Š.: Collect. Czech. Chem. Commun. *40*, 2845 (1975).
5. Floch Ľ., Kováč Š., Vida M.: Collect. Czech. Chem. Commun. *41*, 3580 (1976).
6. Henbest L.: J. Chem. Soc. *1957*, 1965.
7. Katritzky A. R., Lagowski J. M.: Adv. Heterocycl. Chem. *2*, 63 (1963).
8. Reddy G. S., Mandell R., Goldstein J. H.: J. Chem. Soc., *1963*, 1414.
9. Jackmann J. M., Sternhell S.: *Nuclear Magnetic Resonance in Organic Chemistry*, 2nd ed. Pergamon Press, London 1972.
10. Cohen V. I., Poubabass S.: J. Heterocycl. Chem. *14*, 1321 (1977).
11. Gründemann E., Graubaum H., Martin D.· Magn. Reson. Chem. *24*, 21 (1986).
12. Leete E., Kowanko N., Newmark R. A.· J. Am. Chem. Soc. *96*, 4694 (1974).
13. Tranh-Dinh S., Fromageot D.: J. Am. Chem. Soc. *96*, 1484 (1974).
14. Hearman R. A. in: *Carbon-13 NMR Spectral Data, COM-Microfiche Collection of Reference Material* (W. Bremer, L. Arust, B. Franke, R. Gerhards and A. Hazelt, Eds). 4th ed., CNM 35288. Verlag Chemie, Weinheim 1987.
15. Fischer E.: Ber. Dtsch. Chem. Ges. *25*, 2841 (1892).

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