Cyclization of Thiohydrazonate Esters and Azo-Hydrazone Tautomerism of 2-Arylhydrazono-3-oxo-1,4-benzothiazines

Ahmad S. Shawali and Said Elsheikh

Department of Chemistry, Faculty of Science, University of Cairo, Giza, Egypt

Cyril Párkányi

Department of Chemistry and Biochemistry, Florida Atlantic University,
777 Glades Road, P.O. Box 3091, Boca Raton, FL 33431-0991

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Reaction of ethyl arylhydrazonochloroacetates (**1**) with 2-aminothiophenol (**2**) in ethanol in the presence of triethylamine yielded the respective ethyl thiohydrazonate esters (**3**). Similarly, methyl arylhydrazonochloroacetates (**6**) gave the corresponding methyl thiohydrazonate esters (**7**). Treatment of both **3** and **7** with hydrogen chloride in ethanol afforded the respective 1,4-benzothiazine derivatives **4**. Identical products (**4**) were obtained by refluxing **1** or **6** in ethanol in the presence of triethylamine. The structure of **4** was confirmed by their alternate synthesis starting with diethyl chloromalonate in ethanol in the presence of triethylamine which yielded the intermediate 1,4-benzothiazine derivatives **8**. The subsequent coupling of **8** with diazotized anilines in ethanol in the presence of potassium hydroxide afforded **4**.

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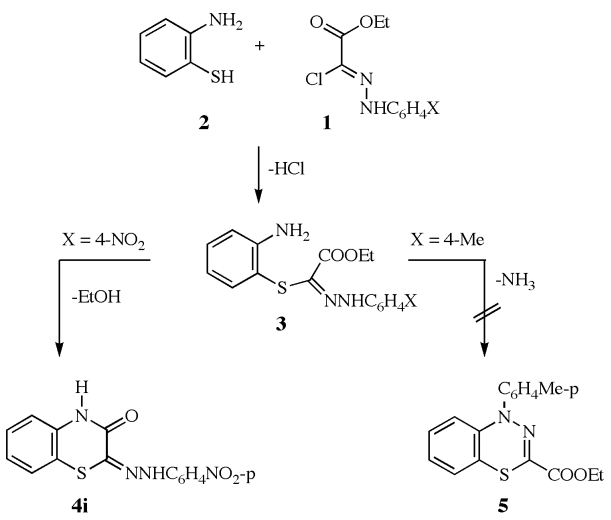
Within the framework of our interest in regioselectivity in cyclization reactions of α-oxohydrazonoyl halides with 1,2-aminothiols [1-4] and azo-hydrazone tautomerism of arylazo derivatives of heterocyclic compounds [5-8], we wish to report the results of our study of the reactions of 2-aminothiophenol (**2**) with a series of ethyl *N*-arylhydrazono-2-chloroacetates (**1**) and elucidation of the tautomeric structures of the respective products. At present, there are two contradicting reports in the literature concerning the structure of the products of such reactions. It has been reported that the reaction of **2** with **1** (X = 4-NO_2) afforded 2,3-dioxo-1,4-benzothiazine-2-(4-nitrophenylhydrazone) **4i** *via* elimination of ethanol from the initially formed thiohydrazonate ester **3** [9]. However, it was also claimed [10] that a similar reaction of **2** with **1** (X = 4-Me) yielded a product that was assigned the structure of 2-ethoxycarbonyl-4-(4-methylphenyl)-1,3,4-benzothiadiazine **5**, obtained by elimination of ammonia from the intermediate **3** (Scheme 1). The latter assignment seems ambiguous, because it involves nucleophilic aliphatic displacement of an amino group from an aromatic amine residue.

This significant difference between the reaction products **4i** and **5** prompted us to re-examine the reactions of **2** with a series of hydrazonoyl chlorides (**1a-1i**) and to study the effect of the ring substituent upon the regioselectivity in the cyclization reaction of thiohydrazonate esters of type **3** (Scheme 2). Also, we have investigated the synthesis of the title compounds **4** by other methods starting from **2** to confirm their structures (Scheme 2). Furthermore, as the title compounds can have more than one tautomeric structure (Chart 1), it was of interest to elucidate their tautomeric structure. For this purpose, the ^{15}N isotopomer of **4d** (**4d'**) was prepared as a typical example of the title compounds, and its ^{1}H and ^{15}N nmr spectra were examined. Because only the hydrazone form **A** can exist with a hydrogen attached to the ^{15}N, a splitting of the proton resonance as well as of the ^{15}N resonance would be a conclusive proof of the existence of the hydrazone form. Finally, the electronic absorption spectra of the compounds under study were investigated in organic solvents of different polarities.

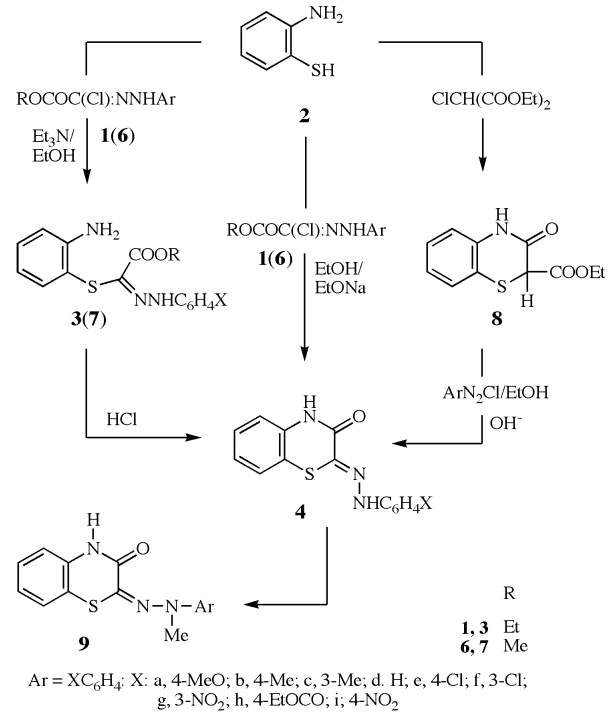
Results and Discussion.

The reaction of 2-aminothiophenol (**2**) with each of the ethyl arylhydrazonochloroacetates **1a-1i** in ethanol in the presence of triethylamine gives ethyl thiohydrazonate esters **3**. Similarly, the use of methyl arylhydrazonochloroacetates **6** instead of **1** in this reaction afforded the respective methyl thiohydrazonate esters **7** (Scheme 2). Treatment of either **3** or **7** with hydrogen chloride in ethanol yielded the respective 1,4-benzothiazine derivatives **4** (Method A). Reaction of **2** with either **1** or **6** in ethanol in the presence of triethylamine under reflux yielded 1,4-benzothiazine derivatives **4** directly (Method B). The identity of the latter products was confirmed by their alternate synthesis. The reaction of diethyl chloromalonate with **2** in ethanol, in the presence of triethylamine under reflux afforded 1,4-benzothiazine derivative **8**. Coupling of the latter with the appropriate diazotized anilines in ethanol in the presence of potassium hydroxide yielded the respective products **4**, *via* the Japp-Klingemann reaction [11] (method C). The products **4** prepared by the latter method proved identical in all respects with those obtained by either of the other two methods (Method A and Method B; Scheme 2). Thus, these results exclude structure **5** previously assigned to the product isolated from the reaction of **2** with **1b** [10].

Scheme 1



Scheme 2



The thiohydrazonate esters **3** (and **7**) were identified by their ir, ^{1}H and ^{13}C nmr, and mass spectra (Tables 1 and 2). For example, their ir spectra (Table 1) revealed the presence of two NH bands in the 3149-3348 cm^{-1} region and a C=O band in the 1655-1707 cm^{-1} region. The ^{1}H nmr spectrum of **3d** shows two singlet signals at δ 9.46 and 4.58 ppm assignable to the NH and NH_2 protons, respectively (Table 2). The ^{13}C nmr spectrum of **3d** shows characteristic signals at δ 163, 62, 14, and 150 ppm that can be assigned to the resonances of carbon atoms in COOEt and C=N-N groups (Table 2). Furthermore, mass spectrum of **3d** contains a characteristic peak at m/e 124 assignable to 2-aminothiophenol (**2**) (Table 1). This is similar to the fragmentation of other aryl and heteroaryl thiohydrazonates whose mass spectra are characterized by the loss of the corresponding arenethiol and heteroarylthiol from their molecular ions, respectively [12].

Table 1

Infrared and Mass Spectra of the Products **3**, **8**, and **9f**

Compound. No.	Infrared spectrum, ν (cm^{-1}) (KBr) Mass spectrum, m/z (rel. intensity, %)
3b	3219, 3165, 1655 329 (13, M$^+$), 208 (28), 122 (73), 106 (100), 91 (29), 77 (87), 65 (30), 53 (41)
3d	3306, 3149, 1699 315 (16, M$^+$), 208 (69), 180 (11), 162 (31), 124 (29), 92 (100), 80 (51), 77 (17), 65 (91)
3g	3348, 3258, 1707 —
3h	3244, 3186, 1701, 1676 —
8	3314, 3200, 1728, 1674 237 (46, M$^+$), 208 (93), 180 (11), 136 (18), 124 (30), 108 (76), 92 (100), 80 (52), 77 (23), 65 (97)
9f	3200, 1641 318 (33, M$^+$), 303 (28), 178 (64), 150 (40), 136 (76), 111 (100), 90 (33), 75 (69), 64 (38), 50 (44)

Table 2

^{1}H and ^{13}C nmr Spectra of the Products **3**, **8**, and **9f**

Compound No.	^{1}H nmr spectrum (δ, ppm, Me_2SO-d_6) ^{13}C nmr spectrum (δ, ppm, Me_2SO-d_6)
3b	1.22 (t, 3H), 2.26 (s, 3H), 4.17 (q, 2H), 5.61 (s, 2H), 6.56-7.36 (m, 8H), 10.47 (s, 1H) 14.1, 20.3, 61.1, 114.0, 114.5, 115.3, 116.9, 125.8, 126.2, 129.6, 130.1, 135.3, 140.5, 149.9, 162.9
3d	1.36 (t, 3H), 4.32 (q, 2H), 4.58 (s, 2H), 6.67-7.40 (m, 8H), 9.46 (s, 1H) 14.1, 61.9, 111.3, 112.1, 115.0, 117.3, 122.3, 124.4, 129.2, 130.3, 135.5, 142.8, 149.5, 162.8
3g	1.28 (t, 3H), 4.50 (q, 2H), 6.63 (s, 2H), 7.05-7.94 (m, 8H), 10.23 (s, 1H) 13.9, 60.9, 107.5, 116.9, 114.3, 116.9, 124.8, 127.6, 129.3, 130.2, 133.8, 143.0, 148.5, 161.6
3h	1.01 (t, 3H), 1.36 (t, 3H), 4.12 (q, 2H), 4.44 (q, 2H), 6.50 (s, 2H), 6.86-7.96 (m, 8H), 10.21 (s, 1H)
8	2.0 (t, 3H), 4.01 (q, 2H), 4.51 (s, 1H), 7.24-7.59 (m, 4H), 10.33 (s, 1H) —
9f	3.59 (s, 3H), 6.96-7.35 (m, 8H), 8.05 (s, 1H) —

The structure of the previously synthesized 1,4-benzothiazine derivative **8** [13-16] was readily identified on the basis of its ir, ^{1}H and ^{13}C nmr, and mass spectra (Tables 1 and 2) and its elemental analysis (Table 3). Its ir spectrum

contains two C=O bands at 1674 and 1728 cm^{-1} and an NH band at 3200-3314 cm^{-1}, in agreement with the literature [14]. In addition to the aromatic proton multiplet at δ 7.24-7.59 ppm, its ^1H nmr spectrum exhibits the following characteristic signals: δ 2.0 (t, 3H), 4.01 (q, 2H), 4.51 (s, 1H), and 10.33 ppm (s, 1H) (Table 2).

Table 3

Synthesized Compounds **3**, **8**, and **9f**

Compound No.	Yield (%)	MP (°C) [a]	Mol. formula (mol. wt.)	Analysis, calcd. (found), % C	H	N
3b	70	200-1 (i)	$C_{17}H_{19}N_3O_2S$ (329.4)	61.98 (61.4)	5.81 (5.5)	12.75 (12.3)
3d	65	108 (i)	$C_{16}H_{17}N_3O_2S$ (315.4)	60.93 (60.7)	5.43 (5.3)	13.32 (13.0)
3g	70	160-2 (ii)	$C_{16}H_{16}N_4O_4S$ (360.4)	53.32 (53.0)	4.47 (4.2)	15.54 (15.1)
3h	75	208 (i)	$C_{19}H_{21}N_3O_4S$ (387.4)	58.89 (58.6)	5.46 (5.2)	10.84 (10.5)
3i	60	137 [b] (i)	$C_{16}H_{16}N_4O_4S$ (360.4)	53.32 (53.0)	4.47 (4.2)	15.54 (15.2)
8	90	144 [c] (i)	$C_{11}H_{11}NO_3S$ (237.2)	55.68 (55.5)	4.67 (4.4)	5.90 (5.7)
9f	45	200 (i)	$C_{15}H_{12}ClN_3OS$ (317.8)	56.69 (56.3)	3.80 (3.6)	13.22 (12.9)

[a] Solvent: i - EtOH, ii - $HCONMe_2$-EtOH. [b] Lit. mp 137 °C [9]. [c] Lit. mp 141-145 °C [14], 142-144 °C [13], 147.5 °C [15].

Table 4

Infrared and ^1H and ^{13}C nmr Spectra of the Products **4a-4i**

Compound No.	Infrared spectrum, ν (cm^{-1}) (KBr) ^1H nmr spectrum (δ, ppm, Me_2SO-d_6) ^{13}C nmr spectrum (δ, ppm, Me_2SO-d_6)
4a	3300, 3225, 1654 3.73 (s, 3H), 6.89-7.36 (m, 8H), 9.73 (s, 1H), 10.98 (s, 1H) 55.2, 114.0, 114.3, 115.2, 116.9, 122.9, 125.7, 127.2, 129.4, 134.3, 138.1, 154.2, 155.4
4b	3296, 3211, 1653 2.25 (s, 3H), 7.07-7.37 (m, 8H), 9.80 (s, 1H), 11.03 (s, 1H) 20.3, 114.0, 114.3, 116.9, 120.3, 122.9, 125.7, 127.2, 129.4, 129.9, 134.3, 142.1, 155.3
4c	3300, 3217, 1653 2.31 (s, 3H), 6.74-7.37 (m, 8H), 9.80 (s, 1H), 11.05 (s, 1H) —
4d [a]	3300, 3217, 1653 [b] 6.93-7.38 (m, 9H), 9.88 (s, 1H), 11.06 (s, 1H) [c] 114.0, 114.2, 117.0, 121.2, 123.0, 125.8, 127.3, 129.0, 134.2, 144.2, 155.2
4d'	3300, 3217, 1653 6.91-7.35 (m, 9H), 9.86 (d, *J* = 93.8, 1H), 10.97 (s, 1H) —
4e	3304, 3213, 1655 7.05-7.38 (m, 8H), 10.10 (s, 1H), 11.11 (s, 1H) 114.0, 115.5, 117.1, 122.3, 123.0, 124.7, 125.8, 127.4, 128.9, 134.1, 143.4, 154.9

Table 4 (continued)

4f	3304, 3209, 1653 6.95-7.39 (m, 8H), 10.06 (s, 1H), 11.16 (s, 1H) —
4g	3290, 3190, 1672 7.11-8.17 (m, 8H), 10.36 (s, 1H), 11.23 (s, 1H) 107.9, 113.7, 115.3, 117.1, 120.1, 123.1, 125.8, 127.4, 130.4, 133.9, 148.6, 154.5
4h	3517, 3445, 1685, 1655 1.32 (t, 3H), 4.28 (q, 2H), 7.10-7.93 (m, 8H), 10.30 (s, 1H), 11.21 (s, 1H) —
4i	3277, 3190, 1678 7.10-8.25 (m, 8H), 10.67 (s, 1H), 11.31 (s, 1H) —

[a] See footnote [c] in Table 6. [b] Lit. gives 3220, 1650 cm^{-1} (nujol) [1a]; 1650 cm^{-1} (nujol) [9]. [c] Lit. gives 9.64 (1H), 10.8 (1H) ppm (Me_2SO-d_6) [9].

Table 5

Electronic Absorption Spectra of Compounds **4a-4i** and **9f**

Compound No.	λ_{max}, nm (log ε) (dioxane)
4a	297 (4.54), 363 (4.81)
4b	290 (4.62), 360 (4.85)
4c	287 (4.58), 356 (4.92)
4d [a]	286 (4.44), 357 (4.67) [b]
4d'	284 (4.09), 354 (4.42) [c]
4e	292 (4.69), 354 (4.97)
4f	292 (4.76), 353 (4.92)
4g	285 (4.70), 349 (5.10)
4h	299 (4.74), 358 (5.08)
4i	276 (4.63), 393 (5.21)
9f	288 (4.48), 351 (4.80)

[a] See footnote [c] in Table 6. [b] λ_{max} (log ε) of **4d** in additional solvents: EtOH, 286 (4.54), 366 (4.76); MeCN, 282 (4.60), 356 (4.86); $CHCl_3$, 286 (4.43), 361 (4.70); Me_2SO, 288 (3.97), 362 (4.26). [c] λ_{max} (log ε) of **4d'** in additional solvents: EtOH, 285 (4.22), 363 (4.46); MeCN, 282 (4.05), 356 (4.40); $CHCl_3$, 286 (4.03), 357 (4.37); Me_2SO, 287 (4.09), 363 (4.41).

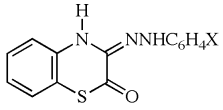
The structures of the final products **4a-4i** were confirmed by their alternate syntheses outlined in Scheme 2, their ir, uv, ^1H and ^{13}C nmr, and mass spectra (Tables 4 and 5), elemental analyses (Table 6), and their reactions. For example, the products **4** were recovered unchanged after treatment with hydrogen peroxide. This finding excludes the isomeric structure **10** [1a]. Structure **5**, previously assigned to the product formed from **1b** and **2** [10], was rejected because the ir spectrum of the isolated products showed an amide band near 1653 cm^{-1} and two NH bands near 3217 and 3300 cm^{-1}. Furthermore, with the exception of **4h**, the ^1H and ^{13}C nmr spectra of the isolated products, **4a-4g** and

Table 6

Synthesized Compounds **4a-4i**

Compound No.	Method [a]	Yield (%)	MP (°C) [b]	Mol. formula (mol. wt.)	Analysis, calcd. (found), % C	H	N	
4a	B	74	240-1 (i)	$C_{15}H_{13}N_3O_2S$ (299.3)	60.18 (60.1)	4.37 (4.2)	14.03 (13.8)	
4b	A, B, C	80	232-3 (ii)	$C_{15}H_{13}N_3OS$ (283.3)	63.58 (63.3)	4.62 (4.5)	14.82 (14.5)	
4c	B	70	249-50 (i)	$C_{15}H_{13}N_3OS$ (283.3)	63.58 (63.4)	4.62 (4.3)	14.82 (14.6)	
4d [c]	A, B, C	75	288 [d] (iii)	$C_{14}H_{11}N_3OS$ (269.3)	62.43	4.11 (62.2)	15.60 (4.1)	(15.3)
4e	B	85	301-2 (iii)	$C_{14}H_{10}ClN_3OS$ (303.7)	55.35 (55.0)	3.31 (3.1)	13.83 (13.5)	
4f	B	85	256-7 (iii)	$C_{14}H_{10}ClN_3OS$ (303.7)	55.35	3.31 (55.1)	13.83 (3.1)	(13.4)
4g	A, B, C	90	268-9 (iii)	$C_{14}H_{10}N_4O_3S$ (314.3)	53.49 (53.2)	3.20 (2.9)	17.82 (17.4)	
4h	A, B	85	244 (iii)	$C_{17}H_{15}N_3O_3S$ (341.3)	59.81	4.42 (59.5)	12.33 (4.1)	(11.9)
4i	A, B	90	303-4 (i)	$C_{14}H_{10}N_4O_3S$ (314.3)	53.49 (53.3)	3.20 (3.1)	17.82 (17.5)	

[a] See the text. [b] Solvent: i - $HCONMe_2$-EtOH; ii - EtOH; iii - $HCONMe_2$. [c] This compound was reported in one of our previous papers [1a] where it was erroneously listed as **7b** while the correct structure is **10b** (Z = S, Ar = Ph). These two latter numbers refer to the numbering in ref. [1a]. [d] Lit. mp 288 °C (dec.) ($HCONMe_2$) [1a]; 277 °C (EtOH) [9].



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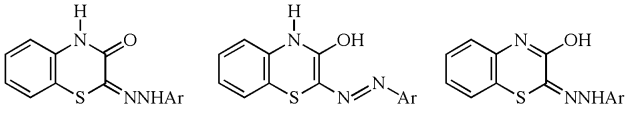
4i, revealed the absence of signals characteristic of the OEt group.

We then turned our attention to the elucidation of the tautomeric form of the products **4**, because, in principle, these compounds can exist in three possible tautomeric forms, **A-C** (Chart 1). To cast some light on the actual tautomeric form(s), we investigated their electronic absorption spectra and compared them with those of azo compounds and hydrazones. A review on the tautomerism in heterocyclic compounds [17] and a paper devoted to the tautomerism of 2-arylhydrazono-1,4,-benzothiazine derivatives with a side chain containing a carboxy group or an ester group in position 3 [18] are available.

Chart 1



A **B** **C**

As shown in Table 5, the electronic absorption spectra of the products **4a-4i** in dioxane reveal two bands in the regions 276-297 nm and 354-393 nm. This indicates that the compounds under study, **4a-4i**, exist in solution predominantly as the hydrazone form **A**, because the absorption pattern is similar to that of typical hydrazones [8,19]. Furthermore, the spectra of the unsubstituted derivative **4d** in different solvents were found to exhibit little if any solvent dependence (Table 5). The observed small shifts of λ_{max} of **4d** in different solvents are due to solvent-solute interactions. Supporting evidence for this observation is the finding that the electronic absorption spectra of arylhydrazones obtained from reactions of quinones with *N*-methyl-*N*-phenylhydrazine, unlike the spectra of *o*- and *p*-hydroxyazo compounds, are basically independent of solvent polarity [8,19].

The assignment of the tautomeric form **A** to the products **4a-4i** was further supported by the similarity of their electronic absorption spectra with that of 2-[*N*-methyl-(3-

chlorophenyl)hydrazono]-3-oxo-1,4-benzothiazine **9f**. The latter compound was prepared in this work by treatment of the product **4f** with methyl iodide in ethanol in the presence of sodium ethoxide (Scheme 2). Its structure was consistent with its spectra (ir, ^{1}H nmr, and mass) and elemental analysis. The ^{1}H nmr spectrum contains a N-Me proton signal at δ = 3.59 ppm. While this chemical shift is similar to that reported for *N*-methyl-*N*-phenylhydrazones (δ = 3.80 ppm) [5a], it is different from that of *N*-methyl cyclic amides (δ = 3.18-3.23 ppm) [20] and 4-methyl-1,4-benzothiazine (δ = 3.13 ppm) [21]. Also, its electronic absorption spectrum in dioxane exhibits two absorption bands at λ_{max} 288 and 351 nm (Table 5) found in the spectra of typical hydrazones [19].

The ^{1}H nmr spectra of the compounds under study, **4a-4i** (Table 4) provide additional evidence that they exist in the hydrazone form **A** rather than the azo forms **B** and **C** (Chart 1). For example, the ^{1}H nmr spectrum of each of the compounds **4a-4i** in deuterated dimethyl sulfoxide exhibits two singlets near δ 9.8 and 11.0-11.3 ppm due to the -NHCO- and =NNH- protons, respectively. This conclusion is substantiated by the literature data [20,22].

Finally, an unambiguous proof of the tautomeric form **A** for **4a-4i** is provided by the ^{1}H nmr spectrum of the ^{15}N-isotopomer **4d'** taken as a typical example of a compound in the series under study. The latter compound was prepared in this work by two different methods. In the first method, ^{15}N-aniline was diazotized in the usual way and the resulting diazonium salt was coupled with ethyl 2-chloro-3-oxobutanoate to give the ^{15}N-isotopomer **1d'**. Reaction of **1d'** with 2-aminothiophenol (**2**) in ethanol in the presence of triethylamine under reflux afforded **4d'** (Method B). Alternatively, diazotized ^{15}N-aniline was coupled with **8** to give **4d'** (Method C). It should be pointed out that there is no possibility of diazonium scrambling during diazotization or coupling reactions [22].

The ^{1}H nmr spectra of ^{15}N-derivative of ethyl phenylhydrazonochloroacetate **1d'** in deuterated dimethyl sulfoxide showed a doublet at δ 10.58 ppm with J = 97 Hz and in deuterated chloroform a doublet at δ 8.37 ppm with J = 94 Hz, respectively. These observations substantiate the above conclusion that no diazonium scrambling occurred and they are consistent with the assigned hydrazone structure **1d'**. Also, in deuterated chloroform, the ^{15}N nmr spectrum of **1d'** contains a doublet centered at δ 149.8 ppm with J = 93.6 Hz.

The ^{1}H nmr spectrum of the ^{15}N-derivative **4d'** in deuterated dimethyl sulfoxide contains a doublet centered at δ 9.86 ppm with J = 93.8 Hz. This indicates that the hydrazone proton is attached to the ^{15}N atom. Because the ^{15}N-H signal separation is so large [22] and because the area of the ^{15}N-H proton signal relative to the aromatic protons was in a 1:9 ratio, compound **4d'** must exist entirely in the hydrazone form **A** under these conditions. Furthermore, the presence of only one ^{15}N-induced doublet in the spectrum of the labeled **4d'** indicates that only the *E*-isomer of the hydrazone form is present in the solvents used.

Thus, on the basis of the above data, it is not unreasonable to conclude that the compounds under study, **4a-4i**, exist predominantly in the hydrazono tautomeric structure **A**.

EXPERIMENTAL

All melting points were determined on a Gallenkamp apparatus and are uncorrected. The infrared (ir) spectra (potassium bromide discs) were obtained on a Pye-Unicam infrared spectrometer. The ^{1}H, ^{13}C, and ^{15}N nmr spectra were recorded in chloroform-*d* and dimethyl-d_6 sulfoxide on a Varian Gemini 300 MHz instrument. Mass spectra were measured on a GCMS-QP 100EX spectrometer (ionizing potential 70 eV). Electronic absorption spectra were recorded in dioxane (and other solvents) on a Shimadzu uv-visible 3101 PC spectrophotometer. Elemental analyses were carried out by the Microanalytical Laboratory of the University of Cairo, Giza, Egypt. ^{15}N-Aniline (95% isotopic purity) was purchased from Merck & Co., Inc., Rahway, NJ, USA.

Ethyl 2-arylhydrazono-2-chloroacetates **1a-1i** [23] and methyl 2-phenylhydrazono-2-chloroacetate **6d** [9] were prepared by direct coupling of arene diazonium chlorides with ethyl 2-chloro-3-oxobutanoate and methyl chloroacetate, respectively, as previously described. The labeled compound **1d'** was prepared by diazotization of ^{15}N-aniline followed by coupling with ethyl 2-chloro-3-oxobutanoate. The physical constants of **1d'** are identical with those of the unlabeled compound **1d** [23].

Preparation of Alkyl 2-Arylhydrazono-2-[(2-aminophenyl)thio]-acetates **3** and **7**.

General Procedure.

To a solution of ethyl 2-chloro-2-arylhydrazonoacetate **1** (10 mmol) in ethanol or acetonitrile (30 mL), 2-aminothiophenol (1.25 g, 10 mmol) and triethylamine (1.4 mL, 1.01 g, 10 mmol) were added. The reaction mixture was stirred for 24 h at room temperature and the solvent was evaporated. Water was added to the residue and the organic product was extracted into chloroform. The chloroform extract was collected, dried over anhydrous sodium sulfate, and filtered. The solvent was then evaporated and the remaining solid residue was collected and crystallized from ethanol to afford the respective thiohydrazonate esters **3**.

When the above procedure was repeated using methyl 2-chloro-2-phenyl-hydrazonoacetate **6d** instead of **1**, the thiohydrazonate ester **7d** was obtained. The synthesized esters **3b**, **3d**, **3g-3i**, together with **8** and **9f**, and their physical constants are listed in Table 3.

Preparation of Ethyl 2,3-Dihydro-3-oxo-4*H*-1,4-benzothiazine-2-carboxylate (**8**).

To a solution of 2-aminothiophenol (**2**, 12.5 g, 0.1 mol) in absolute ethanol (100 mL), diethyl chloromalonate (19.0 g, 0.1 mol) and then triethylamine (19.2 mL, 14.0 g, 0.1 mol) were added. The mixture was stirred for 24 h at room temperature and

then the solvent was evaporated. The residue was dissolved in chloroform and the resulting solution was extracted three times with water. The chloroform layer was separated, dried over anhydrous sodium sulfate, and filtered. The solvent was distilled off, the remaining solid was collected and crystallized from ethanol to give the pure benzothiazine derivative **8** (90% yield). The physical constants of **8** are shown in Table 3.

Preparation of 2,3-Dihydro-2-arylhydrazono-4*H*-1,4-benzothiazin-3-ones (**4**) [9].

Method A.

The appropriate thiohydrazonate ester **3** (0.01 mol) was added to ethanol (30 mL, already saturated with hydrogen chloride) with stirring. The solution was stirred for 3 h at room temperature and the solvent was evaporated. Water was added to the residue and the mixture was neutralized with a solution of sodium bicarbonate. The aqueous solution was extracted with chloroform three times and the extracts were collected, dried over anhydrous sodium sulfate, and filtered. The solvent was distilled off from the filtrate and the remaining solid residue was collected and crystallized from the appropriate solvent to give the respective benzothiazine derivative **4**. Information about these products and their physical constants are summarized in Table 6.

Method B.

To a mixture of equimolar amounts of **1** and 2-aminothiophenol (**2**) (5 mmol each) in ethanol (50 mL), triethylamine (0.96 mL, 0.7 g, 5 mmol) was added with stirring. The mixture was refluxed for 6 h and then cooled. The precipitated solid material was collected by filtration, washed with water, and crystallized from the appropriate solvent (Table 6) to afford the respective benzothiazine derivatives **4**. The physical constants of the compounds obtained by this method are shown in Table 6.

When the same procedure was repeated using the labeled compound **1d'** instead of **1d**, the labeled product **4d'** was obtained in 73% yield (mp 288 °C), with no depression of the mp when mixed with the unlabeled derivative **4d**.

Method C.

To a stirred solution of **8** (1.9 g, 0.01 mol) in ethanol (30 mL), a solution of sodium hydroxide (0.6 g, 0.015 mol) in water (10 mL) was gradually added with stirring. The solution was stirred for an additional 1 h and then chilled in an ice bath at 0-5 °C. A cold solution of the appropriate benzenediazonium chloride was prepared in the usual fashion by diazotization of the respective aniline derivative (0.01 mol) in 6 *M* hydrochloric acid (4 mL) with a solution of 1 *M* sodium nitrite (10 mL). Then the cold solution of the diazonium salt was added to a stirred cold solution of **8** described above. When the addition of the diazonium salt was completed (20 min), the mixture was stirred for 2 h and then left in a refrigerator for 24 h. The precipitated solid was collected by filtration, washed with water, and crystallized from the appropriate solvent to give **4** identical in all respects with the products obtained by methods A and B (Table 6).

Coupling of **8** with diazotized ^{15}N-aniline under the same conditions gave **4d'** - the ^{15}N- isotopomer of **4d**, identical in all respects with that obtained by method A.

Methylation of **4f**.

To an ethanolic solution of sodium ethoxide, prepared by dissolving sodium metal (0.12 g, 5 g-atom) in absolute ethanol (30 mL), compound **4f** (1.5 g, 3 mmol) was added with stirring. Methyl iodide (0.7 g, 5 mmol) was added to the resulting solution, the mixture was refluxed on a water bath for 1 h, and then left in a refrigerator for 24 h. The precipitated solid was collected by filtration, washed with water, dried, and crystallized from ethanol to afford **9f** (Tables 1-3).

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