Behaviour of 5,6-Dihydrothieno[2,3-*h*]cinnolin-3(2*H*)-one and 5,6-Dihydrothieno[3,2-*h*]cinnolin-3(2*H*)-one towards Hydrazine. Synthesis of Thienocinnolinones and of 4-Aminothienocinnolinones

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The isomeric compounds 5,6-dihydrothieno[2,3-*h*]cinnolin-3(2*H*)-one (**7a**) and 5,6-dihydrothieno-[3,2-*h*]cinnolin-3(2*H*)-one (**7b**) rapidly tautomerise to the corresponding 1,4-dihydrothienocinnolinones **8a,b** when kept in refluxing hydrazine hydrate. With longer reaction times the initially formed **8a,b** dehydrogenate to the thienocinnolinones **9a,b** which eventually are aminated to 4-aminothienocinnolinones **10a,b**. This behaviour recalls that reported for the related 5,6-dihydrobenzocinnolin-3(2*H*)-one (**1**) which under the same conditions undergoes dehydrogenation to benzo[*h*]cinnolin-3(2*H*)-one (**2**) followed by 4-amination to **3**, but differs for the stability of the intermediates, for the mechanism of the final amination, and for the higher reaction rate. All these differences can be rationalised in terms of the heats of formation of the intermediates and products of the two series of transformations.

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Introduction.

We have recently reported [1] that 5,6-dihydrobenzo-[*h*]cinnolin-3(2*H*)-one (**1**), when kept in refluxing hydrazine hydrate for 48 hours, underwent a 5,6 dehydrogenation to 76% of benzo[*h*]cinnolin-3(2*H*)-one (**2**) involving an initial tautomerization of **1** to 1,4-dihydrobenzo[*h*]cinnolin-3(2*H*)-one (**1B**). By prolonging the refluxing time to 72 hours, amination of **2** took place, leading to 62% of 4-aminobenzo[*h*]cinnolin-3(2*H*)-one (**3**).

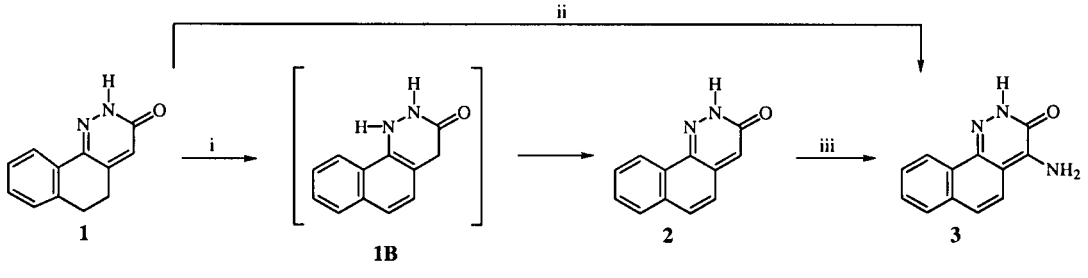
To confirm that the conversion of **1** to **3** occurred through **2**, the latter compound was refluxed in hydrazine hydrate for 24 hours, giving 80% of **3** (Scheme 1).

The somewhat unexpected behaviour of 5,6-dihydrobenzocinnolinone **1** toward hydrazine prompted us to extend the investigation to the isosters 5,6-dihydrothieno-[2,3-*h*]cinnolin-3(2*H*)-one (**7a**) and the isomer 5,6-dihydrothieno[3,2-*h*]cinnolin-3(2*H*)-one (**7b**).

Results and Discussion.

The synthesis of compounds **7a,b** was accomplished by reacting the appropriate thienocyclohexanone **4a,b** with equimolar glyoxylic acid in aqueous sodium hydroxide at room temperature to give the α-hydroxy acids **5a,b** in 42% and 61% yields respectively, which by condensing with hydrazine hydrate in refluxing ethanol for 1.5 hours

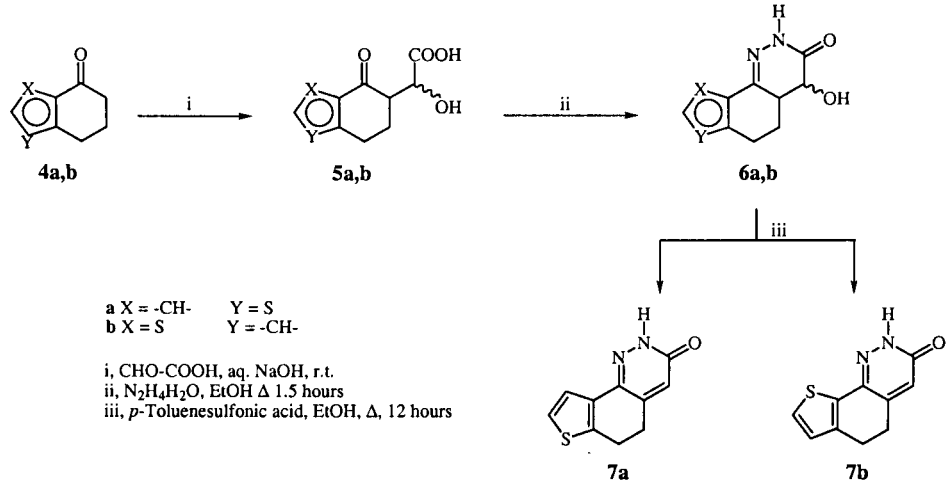
Scheme 1



Reagents: $NH_2NH_2\,H_2O$ excess Δ, 48 hours, (i), 72 hours, (ii), 24 hours (iii).

led to 4-hydroxythienocinnolinones **6a** and **6b** in 66% and 60% yields. Dehydration of **6a,b** with *p*-toluensulphonic acid in refluxing ethanol eventually gave **7a** and **7b** in 80% and 87% yields (Scheme 2).

Scheme 2



When **7a,b** were submitted to reaction with hydrazine hydrate under the conditions employed for **1**, a series of transformations took place which were similar to those reported for **1**, but differed significantly in the stability of the intermediates and in the reaction rates.

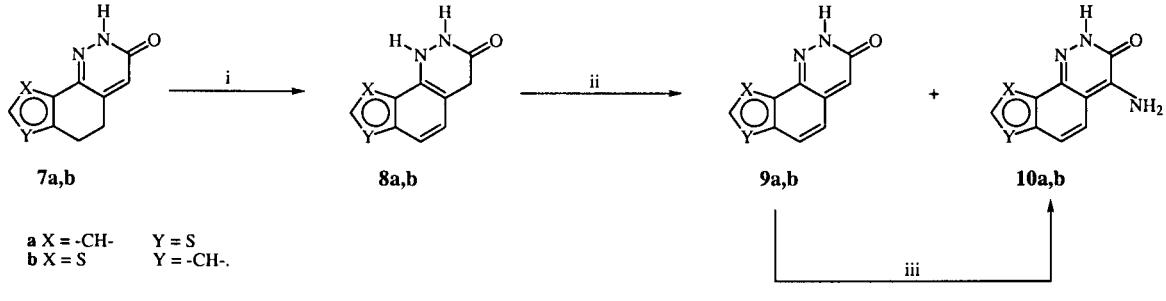
Thus, when **7a** was kept in refluxing hydrazine hydrate for 0.5 hour, it was converted into 80% of a compound **8a** identified as 1,4-dihydrothieno[2,3-*h*]cinnolin-3(2*H*)-one on the basis of elemental and spectroscopic analyses. In particular, its ^{1}H-nmr spectrum was characterised by a singlet at 4.36 δ (H_2-4), an AB system at 7.26 and 7.62 δ (H-5, H-6) and by a deuterium oxide exchangeable broad singlet at 5.40 δ attributable to the NH in positions 1 and 2. By prolonging the reaction time to 3 hours, **8a** underwent a hydrazine induced 5,6-dehydrogenation to thieno[2,3-*h*]cinnolin-3(2*H*)-one (**9a**) followed by 4-amination to **10a** which were isolated in 40% and 35% yields, respectively. The sequence of transformation **8a** → **9a** → **10a** was experimentally confirmed by converting **9a** to **10a** in 70% yield in refluxing hydrazine hydrate for 5 hours. The structures assigned were supported by elemental and spectroscopic analyses. In particular the ^{1}H-nmr of **9a** exhibited a singlet at 7.30 δ (H-4) and an AB system at 7.33 and 7.85 δ (H-5, H-6) while the ^{1}H-nmr of **10a** exhibited a broad singlet at 7.50 δ attributed to the 4-NH_2, besides signals in the range 7.55-7.82 δ assigned to CH in positions 5,6,8,9.

The isomer **7b** similarly reacted with hydrazine, giving rise to the same transformations evidenced for **7a,** with formation in sequence of **8b** → **9b** → **10b** (Scheme 3).

Compounds **7-10**, with the exception of **7a**, are unknown in literature [2].

The hydrazine induced transformations of the thienocinnolinones **7-9** require some comments in the light of the behaviour of benzocinnolinones **1-2**. Though both **1** and **7**, when refluxed in hydrazine hydrate, underwent 5,6-dehydrogenation followed by 4-amination, the reaction rates were found definitely higher for the thieno derivatives **7** (3-5 hours *vs* 48-72 hours). In addition, while in the dehydrogenation of **7** to **9** the intermediates **8** could be isolated in high yield, the formation of a similar intermediate **1B** in the dehydrogenation **1** → **2** was observed [1].

Scheme 3



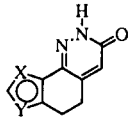
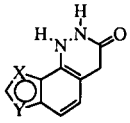
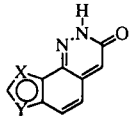
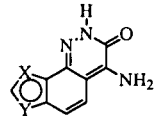
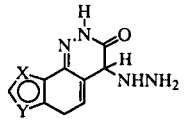
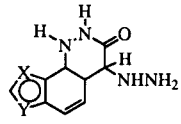
Reagents: $NH_2NH_2H_2O$ excess, Δ 0.5 hour (i), 3 hours (ii), 5 hours (iii).

In order to rationalise the differences in behaviour of benzo and thienocinnolinones we have investigated the relative stability of the starting compounds **1** and **7** and of their hydrazine induced reaction products, by determining their preferred conformation and their heat of formation using a full geometry optimisation carried out with the semiempirical AM1 method [3] at RHF level (Table 1).

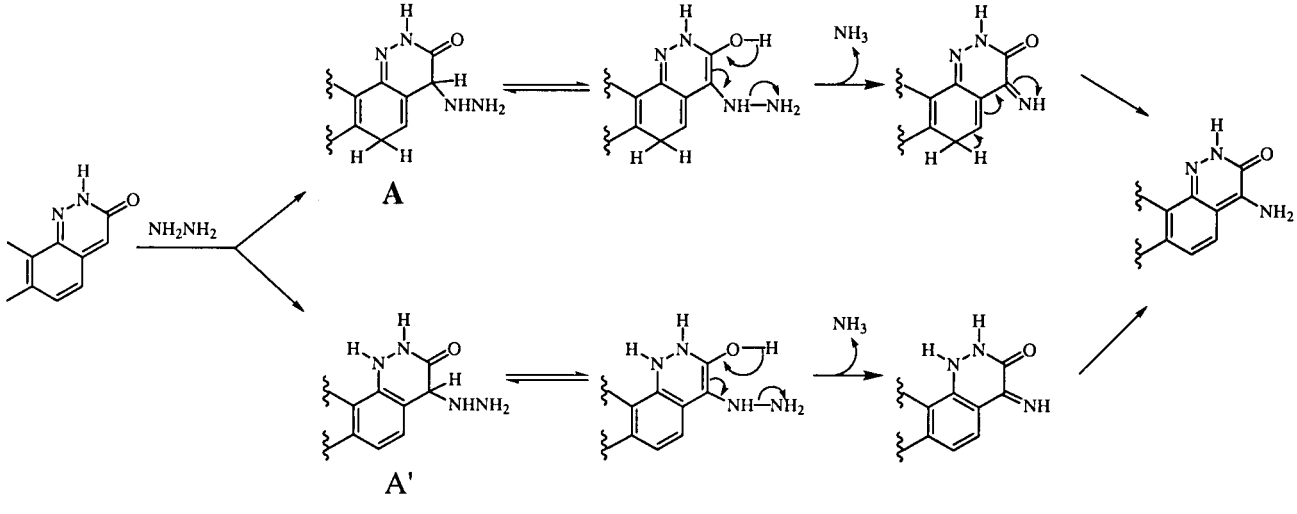
The non-isolation of 1,4-dihydrobenzocinnolinone (**1B**) could be explained by comparing the heats of formation of **1** and **1B** which revealed that **1B** is 3.56 kcal/mol less stable than **1**, with a consequent relative population of the isomers **1B/1** = 0.3:99.7 in a hypothetical equilibrium between them as calculated on the basis of Boltzmann coefficients. Conversely, in the thieno series the isolation of the intermediates **8** could depend on their stability quite similarly to that of starting **7** (see Table 1). In any case, mechanisms involving, respectively, the intermediate **A** or **A'** (Scheme 4).

Actually, as shown in Table 1, calculation of the heat of formation of the possible intermediates revealed that **A** is more stable than **A'** by 2 kcal/mol in the benzocinnolinones series, thus supporting the hypothesis that hydrazine initially adds to the 4,4a,5,6-conjugated system in the conversion of **2** to **3** (see Scheme 3). Conversely, in the thieno series **A'** is more stable than **A** by 1.3-2.3 kcal/mol, thus suggesting the alternative reaction path with initial addition to the 4,4a,9b,1-conjugated system. Interestingly, the mechanism of amination **9** → **10** involving **A'** as an intermediate, closely recalls that hypothesised by Singh [4] for the 4-amination of 6-arylpyridazinones. However, this mechanism seems not operative in the amination of **2** to **3** not only on the basis of the heats of formation of **A** and **A'**, but also because of the observed failure of the indenopyridazinone [1], a lower homologue of **1**, to give 4-amination in refluxing hydrazine hydrate. In addition, it is also noted that the reaction rates for the conversion **9** → **10** appear much higher than the corresponding conversion of **2** to **3**. This difference can be the result of the greater solubility of **9** with respect to **2**

Table 1
Heat of Formation (kcal/mol) of Compounds and Intermediates

X	Y						
CH	CH = CH	32.42 (**1**)	35.98 (**1B**)	55.75 (**2**)	52.70 (**3**)	66.61 (**A**)	68.60 (**A'**)
CH	S	37.72 (**7a**)	36.86 (**8a**)	59.62 (**9a**)	56.45 (**10a**)	71.42 (**A**)	69.18 (**A'**)
S	CH	37.10 (**7b**)	37.10 (**8b**)	59.33 (**9b**)	56.21 (**10b**)	70.39 (**A**)	69.03 (**A'**)

Scheme 4



independent of the stability of the intermediates, the same reaction mechanism can be hypothesised for the hydrazine induced dehydrogenation of the benzo and thieno cinnolinones, **1** → **2** respectively **7** → **9**. However, this does not seem true for the final 4-amination. In principle, the initial hydrazine addition both to benzo **2** and thienocinnolinones **9** could take place by two possible

under the reaction conditions (see Experimental) and/or might depend on the relative stability of intermediates **A** (in the case of **2**) and **A'** (in the case of **9**).

EXPERIMENTAL

Hydrazine hydrate was employed as pure hydrazine monohydrate. Melting points were determinate with a Büchi 510 capillary apparatus and are uncorrected. The ^{1}H-nmr spectra were recorded on a Varian Gemini 200 spectrometer; chemical shifts are reported as δ (ppm) relative to tetramethylsilane as the internal standard; dimethylsulfoxide-d_6 was used as the solvent, unless otherwise noted. The ir spectra were recorded on a Perkin Elmer 781 spectrometer and registered in nujol mulls, unless otherwise noted. The tlc on silica gel plates were used to check product purity. Silica gel 60 (Merck 230-400 mesh) was used for column flash chromatography. The elemental analyses indicated are within ± 0.4 of theoretical values.

Compounds **5a,b, 6a,b** were isolated as diastereomeric mixtures (^{1}H-nmr).

α–Hydroxy-α–(4-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophen-5-yl)acetic Acid (**5a**).

To an ice-cooled mixture of **4a** (3 g, 0.020 mole) and glyoxylic acid monohydrate (2.07 g, 0.022 mole) vigorously stirred in water (50 ml), a solution of sodium hydroxide (2.46 g, 0.06 mole) in water (50 ml) was added. After stirring for 1 hour at room temperature, the alkaline solution was washed with ether (25 ml) and then was acidified with concentrated hydrochloric acid on cooling. After stirring at room temperature overnight, the product that separated was filtered, washed with water and dried to give **5a** (1.9 g, 42%) mp 159-160° (lit [2]. 164-166°); ir: ν/cm^{-1} 3280, 1750, 1730, 1640; ^{1}H-nmr: 2.01-2.54 (m, 2H H-6); 2.88-3.50 (m, 4H H-5, H-7 and OH deuterium oxide exchangeable); 4.31 and 5.06 (2d, 1H C_α-H); 7.10-7.55 (m, 2H H-2, H-3); 8.5 (br. s, 1H COOH deuterium oxide-exchangeable).

α-Hydroxy-α-(7-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophen-5-yl)acetic Acid (**5b**).

It was prepared as reported for **5a**, starting from the required **4b**, yield 61%, mp 174-176°; ir: ν/cm^{-1} 3300, 1750, 1730, 1640; ^{1}H-nmr: 1.8-2.30 (m, 2H H-5); 2.50-3.15 (m, 4H H-4, H-6 and OH deuterium oxide exchangeable), 4.30 and 4.76 (2d, 1H C_α-H), 7.08-7.22 (m, 1H, H-3), 7.95-8.13 (m, 1H, H-2).

Anal. Calcd. for $C_{10}H_{10}O_4S$: C, 53.10; H, 4.46; S, 14.15. Found: C, 53.29; H, 4.13; S, 13.97.

4-Hydroxy-4,4a,5,6-tetrahydrothieno[2,3-*h*]cinnolin-3(2*H*)-one (**6a**).

A solution of **5a** (5.1 g, 0.023 mole) and hydrazine hydrate (1.25 g, 0.024 mole) in ethanol (15 ml) was refluxed for 1.5 hours. After cooling, the product was filtered, washed with cold ethanol and dried to give **6a** (3.0 g, 60%), mp 250° (ethanol) (lit [2]. 251-253°); ir: ν/cm^{-1} 3420, 3200, 1670; ^{1}H-nmr: 1.7-2.10 (m, 1H H-4_a), 2.40-3.11 (m, 4H H-5, H-6), 3.90 (dd, 1H H-4), 5.65 and 6.08 (2d, 1H OH deuterium oxide-exchangeable), 7.25 (AB d, 1H H-9 J = 5.4 Hz), 7.35 (AB d, 1H H-8 J = 5.4 Hz), 10.81 (bs, 1H NH deuterium oxide-exchangeable).

4-Hydroxy-4,4a,5,6-tetrahydrothieno[3,2-*h*]cinnolin-3(2*H*)-one (**6b**).

It was prepared as reported for **6a**, starting from the required **5b**, yield 66%, mp 205° dec; ir: ν/cm^{-1} 3380, 3320, 1665; ^{1}H-nmr: 1.50-1.95 (m, 1H H-4_a), 2.30-2.98 (m, 4H H-5, H-6), 3.80-4.05 (m, 1H H-4), 5.62 and 6.10 (2d, 1H OH deuterium oxide-exchangeable), 6.97 (ABd, 1H H-7 J = 4.8 Hz), 7.56 (ABd, 1H H-8 J = 4.8 Hz), 10.81 (bs, 1H NH deuterium oxide-exchangeable).

Anal. Calcd. for $C_{10}H_{10}N_2O_2S$: C, 54.05; H, 4.53; N, 12.26; S, 14.40. Found: C, 54.65; H, 4.13; N, 12.35; S, 14.21.

5,6-Dihydrothieno[2,3-*h*]cinnolin-3(2*H*)-one (**7a**).

A solution of **6a** (3 g, 13.5 mmoles) and *p*-toluenesulfonic acid (3 g, 15.7 mmoles) in ethanol (30 ml) was refluxed for 12 hours. After cooling, the product was filtered, washed with ethanol and dried to give **7a** (2.4 g, 87%), mp 250° dec (lit [2], mp 270°); ir: ν/cm^{-1} 3400, 1680, 1580, 1550; ^{1}H-nmr: 2.90-3.10 (m, 4H H-5, H-6), 6.71 (s, 1H H-4), 7.23 (ABd, 1H H-8 J = 5.4 Hz), 7.38 (ABd, 1H H-9 J = 5.4 Hz), 12.71 (bs, 1H NH deuterium oxide-exchangeable).

Anal. Calcd. for $C_{10}H_8N_2OS$: C, 58.82; H, 3.95; N, 13.72; S, 15.67. Found: C, 58.42; H, 3.78; N, 13.91; S, 15.73.

5,6-Dihydrothieno[3,2-*h*]cinnolin-3(2*H*)-one (**7b**).

It was prepared as reported for **7a**, starting from the required **6b**, yield 80%, mp 222° dec; **7b** was also obtained in 61% yield from **5b** in hydrazine hydrate (1:3) in ethanol at reflux for 4 hours; ir: ν/cm^{-1} 3120, 3050, 1670, 1600, 1580, 1550; ^{1}H-nmr: 2.80-3.01 (m, 4H H-5, H-6), 6.83 (s, 1H H-4), 7.07 (ABd, 1H H-7 J = 5.2 Hz), 7.60 (ABd, 1H H-8 J = 5.2 Hz), 12.70 (bs, 1H NH deuterium oxide-exchangeable).

Anal. Calcd. for $C_{10}H_8N_2OS$: C, 58.82; H, 3.95; N, 13.72; S, 15.67. Found: C, 58.61; H, 3.87; N, 13.31; S, 15.27.

1,4-Dihydrothieno[2,3-*h*]cinnolin-3(2*H*)-one (**8a**).

A mixture of **7a** (1 g, 4.9 mmoles) and hydrazine hydrate (5 ml) was refluxed for 0.5 hours. After cooling, the solid was filtered, washed with water and dried to give **8a** (0.8 g, 80%), mp 270° dec; ir: ν/cm^{-1} 3350, 3300, 3100, 1720, 1640, 1540; ^{1}H-nmr: 4.36 (s, 2H H-4), 5.40 (s, 2H NH deuterium oxide-exchangeable), 7.26 (d, 1H H-5 J = 8 Hz), 7.62 (d, 1H H-6 J = 8 Hz), 7.71 (d, 1H H-8 J = 5.3 Hz), 8.12 (d, 1H H-9 J = 5.3 Hz).

Anal. Calcd. for $C_{10}H_8N_2OS$: C, 58.82; H, 3.95; N, 13.72; S, 15.67. Found: C, 58.76; H, 3.91; N, 13.69; S, 15.53.

1,4-Dihydrothieno[3,2-*h*]cinnolin-3(2*H*)-one (**8b**).

It was prepared as reported for **8a**, starting from the required **7b** and refluxed for 15 minutes, yield: 80%, mp 213-215° dec; ir: ν/cm^{-1} 3300, 1700, 1640; ^{1}H-nmr: 3.70 (s, 2H H-4); 5.40 (s, 2H, NH deuterium oxide-exchangeable), 7.26 (d, 1H H-5 J = 8.8 Hz), 7.43 (d, 1H H-7 J = 5.5 Hz), 7.51 (d, 1H H-6 J = 8.8 Hz), 7.7 (d, 1H H-8 J = 5.5 Hz).

Anal. Calcd. for $C_{10}H_8N_2OS$: C, 58.82; H, 3.95; N, 13.72; S, 15.67. Found: C, 58.95; H, 3.98; N, 13.99; S, 15.31.

Thieno[2,3-*h*]cinnolin-3(2*H*)-one (**9a**) and 4-Aminothieno-[2,3-*h*]cinnolin-3(2*H*)-one (**10a**).

A mixture of **8a** (1 g, 4.9 mmoles) and hydrazine hydrate (5 ml) was refluxed for 4 hours. After cooling, the solid was filtered, washed with water and purified by silica gel flash chromatography eluting with chloroform/methanol 9:1 to give **10a** (0.37 g, 35%), mp 330° dec; ir: ν/cm^{-1} 3450, 3320, 3180, 1640,

1620, 1600; ^{1}H-nmr: 7.5 (s, NH_2 deuterium oxide-exchangeable), 7.55 (d, 1H H-5 J = 9 Hz), 7.7 (d, 1H H-6 J = 9 Hz), 7.76-7.82 (m, 2H H-8 H-9), 13.2 (s, 1H NH deuterium oxide-exchangeable).

Anal. Calcd. for $C_{10}H_7N_3OS$: C, 55.30; H, 3.25; N, 19.35; S, 14.73. Found: C, 55.26; H, 3.18; N, 19.31; S, 14.52.

The filtrate was evaporated to dryness, the residue was triturated with chloroform and filtered to give **9a** (0.4 g, 40%), mp 230°; ir: ν/cm^{-1} 3200, 1660, 1640, 1600; ^{1}H-nmr: 7.30 (s, 1H H-4); 7.33 (d, 1H H-5 J = 8.6 Hz), 7.85 (d, 1H H-6 J = 8.6 Hz), 7.89-7.94 (m, 2H H-8 H-9), 13.0-13.6 (s all., 1H NH deuterium oxide-exchangeable).

Anal. Calcd. for $C_{10}H_6N_2OS$: C, 59.40; H, 2.99; N, 13.86; S, 15.83. Found: C, 59.36; H, 2.89; N, 13.87; S, 15.95.

Compound **10a** was also obtained in 67% yield by refluxing a mixture of **9a** (4.5 mmoles) and hydrazine hydrate (5 ml) for 5 hours.

Thieno[3,2-*h*]cinnolin-3(2*H*)-one (**9b**) and 4-Aminothieno[3,2-*h*]cinnolin-3(2*H*)-one (**10b**).

It was prepared as reported for **9a**, starting from the required **8b**, yield, **10b** 30%, mp 270° dec; ir: ν/cm^{-1} 3410, 3320, 3280, 1620, 1580; ^{1}H-nmr: 7.40 (d, 1H H-5 J = 9 Hz), 7.44 (d, 1H H-7 J = 5.4 Hz), 7.58 (bs, 2H, NH_2 deuterium oxide-exchangeable), 7.72 (d, 1H H-6 J = 9 Hz), 7.77 (d, 1H H-8 J = 5.4 Hz), 13.0 (s, 1H NH deuterium oxide-exchangeable).

Anal. Calcd. for $C_{10}H_7N_3OS$: C, 55.30; H, 3.25; N, 19.35; S, 14.73. Found: C, 54.94; H, 3.36; N, 19.27; S, 14.67.

Compound **9b** had yield, 55%, mp 285° dec; ir: ν/cm^{-1} 1700, 1680, 1600; ^{1}H-nmr: 7.37 (s, 1H H-4); 7.32 (d, 1H H-5 J = 10 Hz), 7.55 (d, 1H H-7 J = 5.7 Hz), 7.74 (d, 1H H-6 J = 10 Hz), 7.86 (d, 1H H-8 J = 5.7 Hz), 13.0-13.6 (s all., 1H NH deuterium oxide-exchangeable). Compound **10b** was also prepared as reported for **10a**, starting from the required **9b**, yield: 70%.

Anal. Calcd. for $C_{10}H_6N_2OS$: C, 59.40; H, 2.99; N, 13.86; S, 15.83. Found: C, 59.62; H, 2.97; N, 13.74; S, 15.51.

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