Condensed 1,2,4-Triazines. Regioselective Condensations With Benzo[*h*]quinoline-5,6-dione

Mohga M. Eid, Mohamed A. Badawy and Yehia A. Ibrahim*

Department of Chemistry, Faculty of Science, Cairo Univeristy,
Giza, A. R. Egypt

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Benzo[*h*]quinoline-5,6-dione condenses with semicarbazide and its derivatives regioselectively at the 6-position and the products cyclize into the corresponding condensed 1,2,4-triazines. Reactions of the obtained triazines with a variety of reagents are described.

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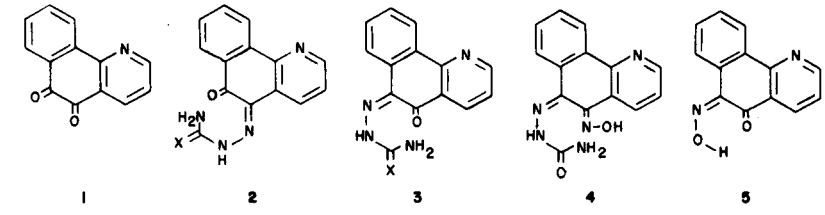
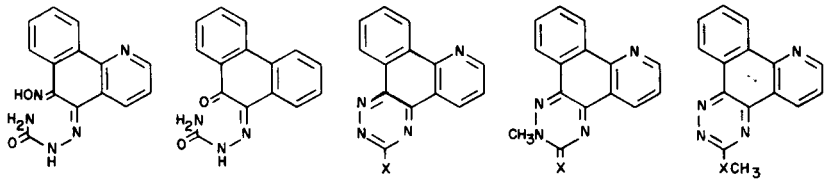
Due to the pronounced biological activity of condensed 1,2,4-triazines [1-5], our interest has, now, been extended to investigate the synthesis and reaction of some new derivatives of this system. Thus, benzo[*h*]quinoline-5,6-dione (**1**) [6] was condensed with semicarbazide hydrochloride and with thiosemicarbazide in glacial acetic acid to give the monosemicarbazone and the monothiosemicarbazone respectively. Of the two possible isomeric condensation products **2a,b** and **3a,b**, only one isomer was identified (tlc) in each case. Structure **3** is more plausible for the condensation products since the C=O group in compound **1** in position 6 is more electrophilic than the C=O group in position 5 due to the attachment of the latter group to the 3-position of the pyridine ring. The pyridine ring by its inductive effect (—I effect) decreases the polarization of the C=O group at position 5 and this effect becomes more pronounced in acidic medium due to the protonation of the nitrogen atom of the pyridine ring. Also infrared comparison of the monosemicarbazone **3** and that of phenthraquinone monosemicarbazone (**7**) showed carbonyl absorption bands at 1710 and 1725 cm^{-1} respectively. This comparison shows differences in the nature of the carbonyl groups of these two monosemicarbazones and this may be taken as an evidence in favor of structure **3** over structure **2**.



1 **2** **3** **4** **5**

a, X = O
b, X = S



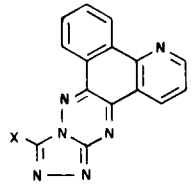
6 **7** **8** **9**, X = O **10**, X = O

a, X = OH, b, X = SH
c, X = NH_2, d, X = Cl

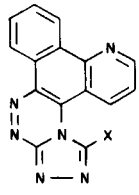
11, X = S **12**, X = S

13, X = NHR

a, R = C_6H_5, b, R = $C_6H_4CH_3$-p
c, R = $C_6H_4OCH_3$-p
d, R = NH_2
e, R = N=$CHC_6H_4OCH_3$-p
f, R = N=$CHC_6H_3(OCH_3)_2$-3,4



14, X = H
17, X = SH



15, X = H

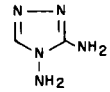


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Table

Products	Mp °C	Yield %	Formula (MW)	Analysis % Calcd./Found C	H	N	S	Cl
3a	229	61	$C_{14}H_{10}N_4O_2$	63.15	3.78	21.04		
			(266.25)	62.80	4.10	21.30		
3b	228	52	$C_{14}H_{10}N_4SO$	59.56	3.57	19.84	11.36	
			(282.31)	60.00	3.40	20.20	11.60	
4	220	85	$C_{14}H_{11}N_5O_2$	59.77	3.94	24.90		
			(281.27)	60.00	4.00	24.70		
5	178	65	$C_{13}H_8N_2O_2$	69.63	3.59	12.49		
			(224.21)	69.90	3.70	12.80		
6	279	91	$C_{14}H_{11}N_5O_2$	59.77	3.94	24.90		
			(281.27)	59.80	4.30	25.00		
8a	302	72	$C_{14}H_8N_4O$	67.73	3.24	22.57		
			(248.23)	67.50	3.20	22.50		
8b	288	78	$C_{14}H_8N_4S$	63.62	3.05	21.20	12.13	
			(264.29)	63.60	2.90	21.40	12.20	
8c	310	84	$C_{14}H_9N_5$	68.00	3.66	28.32		
			(247.25)	67.80	3.70	28.50		
8d	213	99	$C_{14}H_7ClN_4$	63.04	2.65	21.00		13.30
			(266.68)	62.60	3.00	21.00		13.10
9	262	37	$C_{15}H_{10}N_4O$	68.69	3.84	21.36		
			(262.26)	68.80	4.00	21.20		
12	243	90	$C_{15}H_{10}N_4S$	64.72	3.62	20.13	11.52	
			(278.32)	64.60	3.90	20.20	11.10	
13a	313	83	$C_{20}H_{13}N_5$	74.29	4.05	21.66		
			(323.34)	74.40	3.70	22.00		
13b	311	82	$C_{21}H_{15}N_5$	74.76	4.48	20.76		
			(337.37)	74.50	4.50	21.00		
13c	313	85	$C_{21}H_{15}N_5O$	71.37	4.28	19.82		
			(353.37)	71.50	4.50	19.50		
13d	242	99	$C_{14}H_{10}N_6$	64.11	3.84	32.04		
			(262.27)	64.40	4.00	32.10		
13e	310	99	$C_{22}H_{16}N_6O$	69.46	4.24	22.09		
			(380.40)	69.50	4.40	22.40		
13f	305	99	$C_{23}H_{18}N_6O_2$	67.30	4.42	20.48		
			(410.42)	67.60	4.40	20.70		
14	5311	95	$C_{15}H_8N_6$	66.17	2.96	30.87		
			(272.26)	66.50	2.80	30.90		
17	326	80	$C_{15}H_8N_6S$	59.19	2.65	27.61	10.53	
			(304.32)	59.30	2.50	27.30	10.70	

Condensation of the semicarbazone **3a** with hydroxylamine hydrochloride gave the oxime semicarbazone **4** which is different from the isomer **6** obtained by reversing the order of condensation.

Compounds **3a** and **3b** were cyclized in 5% aqueous potassium hydroxide solution into 3-hydroxy- and 3-mercapto-1,2,4-triazino[6,5-*f*]benzo[*h*]quinolines (**8a** and **8b**) respectively.

3-Amino-1,2,4-triazino[6,5-*f*]benzo[*h*]quinoline (**8c**) was obtained, directly, by condensing the dione **1** with aminoguanidine bicarbonate in glacial acetic acid or in ethanol in the presence of a few drops of hydrochloric acid.

Compounds **8a** and **8b** underwent methylation with dimethyl sulfate in 5% aqueous potassium hydroxide solution. The products obtained are the 2*N*-methyl derivative **9** (and not the 3-*O*-methyl derivative **10**) and the 3-*S*-methyl derivative **12** (and not the 2-*N*-methyl derivative **11**) respectively. The proposed structure for **9** is supported by the ir spectrum which shows a strong band at 1675 cm^{-1} characteristic of a ring C=O group. The structure of **12** was evidenced by its ready hydrolysis to compound **8a** upon heating in an alcoholic hydrochloric acid solution.

3-Chloro-1,2,4-triazino[6,5-*f*]benzo[*h*]quinoline (**8d**) was prepared by heating **8a** with phosphorus oxychloride at 150° for 1½ hours. Compound **8d** was readily converted to the 3-arylamino derivatives **13a-c** upon heating with the appropriate arylamine at their boiling point for 5 minutes. The 3-hydrazino derivative was obtained by heating under reflux either of compounds **8b** or **8d** with hydrazine hydrate in pyridine. Compound **13d** underwent condensation with aromatic aldehydes to give the corresponding triazinylhydrazones **13e-f**. Cyclocondensation of **13d** with formic acid led to the formation of 1,2,4-triazolo[3,4-*b*]-1,2,4-triazino[6,5-*f*]benzo[*h*]quinoline (**14**). The structure of compound **14** was confirmed by independent synthesis by

heating under reflux compound **1** with 3,4-diamino-1,2,4-triazole (**16**) [7]. This also excludes structure **15** for this cyclocondensation product.

Similarly, 3-mercapto-1,2,4-triazolo[3,4-*b*]-1,2,4-triazino-[6,5-*f*]benzo[*h*]quinoline (**17**) was obtained either by heating compound **13d** in pyridine with carbon disulfide or by heating an intimate mixture of compound **13d** and thiourea at 220° until no ammonia was evolved.

EXPERIMENTAL

All melting points are uncorrected. The ir spectra (potassium bromide) were recorded with a Unicam SP 1200 infrared spectrophotometer.

Benzo[*h*]quinolin-5,6-dione 6-Monosemicarbazone (**3a**).

A solution of the dione **1** (0.01 mole) and semicarbazide hydrochloride (0.01 mole) in acetic acid (5 ml) was heated under reflux for 15 minutes. The reaction mixture was cooled and diluted with water. The precipitate was filtered and crystallized from butanol as yellow needles of **3a** (Table).

Benzo[*h*]quinolin-5,6-dione 6-Monothiosemicarbazone (**3b**).

A solution of the dione **1** (0.01 mole) and thiosemicarbazide (0.01 mole) in acetic acid (5 ml) was heated under reflux for 5 minutes. After cooling the precipitate was collected and recrystallized from nitrobenzene as red needles of **3b** (Table).

Benzo[*h*]quinolin-5,6-dione 6-Monoxime (**5**).

A mixture of the dione **1** (0.01 mole) and hydroxylamine hydrochloride (0.01 mole) in ethanol (30 ml) and chloroform (15 ml) was heated under reflux for 1 hour. The reaction mixture was then concentrated to 15 ml, cooled and the precipitated crystals were then collected and recrystallized from ethanol into yellow crystals of **5** (Table).

Action of Semicarbazide Hydrochloride on Compound **5**.

A mixture of compound **5** (0.01 mole) and semicarbazide hydrochloride (0.01 mole) in ethanol (20 ml) and water (10 ml) was heated under reflux for 6 hours. The precipitated crystals formed upon cooling were collected and recrystallized from acetic acid as yellow crystals of **4** (Table).

Action of Hydroxylamine Hydrochloride on Compound **3a**.

The previous method was followed. The precipitate obtained was collected and recrystallized from butanol as brown crystals of **6** (Table).

3-Hydroxy-1,2,4-triazino[6,5-*f*]benzo[*h*]quinoline (**8a**).

Compound **3a** (2.0 g) was dissolved in 5% aqueous potassium hydroxide (100 ml). The solution was heated under reflux for 1½ hour, filtered, cooled and then acidified with acetic acid. The precipitate was collected and crystallized from dimethylformamide into red crystals of **8a** (Table).

3-Mercapto-1,2,4-triazino[6,5-*f*]benzo[*h*]quinoline (**8b**).

Compound **3b** (2.0 g) was dissolved in 5% aqueous potassium hydroxide (100 ml). The solution was heated under reflux for ½ hour, filtered, cooled and then acidified with acetic acid. The precipitate was collected and crystallized from dimethylformamide into red crystals of **8b** (Table).

3-Amino-1,2,4-triazino[6,5-*f*]benzo[*h*]quinoline (**8c**).

A mixture of the dione **1** (0.01 mole) and aminoguanidine bicarbonate (0.01 mole) in either acetic acid (10 ml) or abosolute ethanol (15 ml) and 3 drops concentrated hydrochloric acid, was heated under reflux for 3 hours. After cooling the precipitate was collected and recrystallized from pyridine into yellow crystals of **8c** (Table).

Action of Dimethyl Sulfate on **8a,b**.

Each of compounds **8a,b** (0.005 mmole) was dissolved in 5% aqueous potassium hydroxide solution (25 ml), then dimethyl sulfate (0.006 mole) was added. The reaction mixture was stirred for 30 minutes, then left overnight at room temperature. The precipitate was collected and recrystallized from pyridine into green crystals of **9** and from nitrobenzene into yellow crystals of **11**, respectively (Table).

Action of Hydrochloric Acid on **11**.

A mixture of compound **11** (0.005 mole) and 15 ml alcoholic solution containing hydrochloric acid (3 ml) was heated under reflux for 2 hours and then cooled. The precipitate obtained was recrystallized from dimethylformamide and proved identical with compound **8a** (mixed mp and ir spectra).

3-Chloro-1,2,4-triazino[6,5-*f*]benzo[*h*]quinoline (**8d**).

Compound **8a** (0.005 mole) and phosphorus oxychloride (2.4 ml) were heated together at 140-150° for 1½ hours. After cooling the mixture was poured over crushed ice. The precipitate was then cooled and recrystallized from dimethylformamide into yellow crystals of **8d** (Table).

Action of Amines on **8d**.

A mixture of **8d** (0.002 mole) and the appropriate amine (1.2 g) were heated under reflux for 5 minutes, then cooled, and the precipitate was washed with alcohol and recrystallized from dimethylformamide into crystals of **13a-c** (Table).

3-Hydrazino-1,2,4-triazino[6,5-*f*]benzo[*h*]quinoline (**13d**).

Either of compounds **8b** or **8d** (0.005 mole) was heated under reflux with hydrazine hydrate (3 ml, 99%) and pyridine (5 ml) for ½ or 1½ hours respectively. The precipitate was collected and recrystallized from dimethylformamide into yellow crystals of **13d** (Table).

Action of Aromatic Aldehydes on **13d**.

Compound **13d** (0.002 mole) was heated under reflux with the appropriate aromatic aldehyde (0.002 mole) in ethanol (10 ml) for 30 minutes. The solid obtained was recrystallized from dimethylformamide as orange or orange red crystals of **13e,f** (Table).

1,2,4-Triazolo[3,4-*b*]-1,2,4-triazino[6,5-*f*]benzo[*h*]quinoline (**14**).

(a) To compound **13d** (0.002 mole) was added formic acid (3 ml, 85%), and the reaction mixture was heated under reflux for 5 hours, cooled and poured over crushed ice. The residue was collected and crystallized from dimethylformamide as orange yellow crystals of **14** (Table).

(b) To a solution of the dione **1** (0.001 mole) in ethanol (20 ml) was added 3,4-diaminotriazole (0.001 mole). The reaction mixture was heated under reflux for ½ hour, then potassium hydroxide (0.1 g) was added, then heating was continued for a further ½ hour. After cooling crystals of compound **14** was collected and recrystallized from dimethylformamide (Table).

3-Mercapto-1,2,4-triazolo[3,4-*b*]-1,2,4-triazino[6,5-*f*]benzo[*h*]quinoline (**17**).

(a) Compound **13d** (0.002 mole) was heated under reflux in pyridine (5 ml) with carbon disulfide (0.5 ml) for 1 hour, during which time hydrogen sulfide was evolving and a reddish brown precipitate separated. After cooling the precipitate was collected and recrystallized from dimethylformamide into reddish brown crystals of **17** (Table).

(b) An intimate mixture of **13d** (0.5 g) and thiourea (1 g) was heated at 220° until no ammonia evolved. The product obtained was cooled, dissolved in 5% potassium carbonate solution, filtered and acidified with concentrated hydrochloric acid. The precipitate was collected and crystallized from dimethylformamide as reddish brown crystals of **17** (Table).

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