113. Condensed 1,2,4-Triazines I: Behaviour of Phenanthro[9,10-*e*]-1,2,4-triazine Derivatives Towards Alkylating and Reducing Agends, *Grignard* Reagents, and Amines

by **Mohamed Mohamed Mohamed Sallam, Yehia Abdu Ibrahim,** and **Sayed Abdel-Latif Abdel-Hady**

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

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Summary. Alkylation of 3-hydroxy-phenanthro[9,10-*e*]1,2,4-triazine (**1a**) yielded the N(2)-alkyl derivatives **2a–2b**; alkylation of the 3-mercapto analogue **1b** yielded the S-alkyl derivatives **1f–1i**.

1a–1b reacted with alkyl and aralkylmagnesium halides to yield the corresponding 3-hydroxy-, and 3-mercapto-5-alkyl-(aralkyl)-phenanthro[9,10-*e*]2,3,4,5-tetrahydro-1,2,4-triazines **5a–5f**.

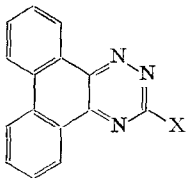
Reduction of **1a** yielded the hexahydrotriazine derivative **7**. Amination of **1c** yielded the 3-amino derivatives **1j–1o** after prolonged heating.

In continuation of the study of the biological activity of 1,2,4-triazines [1], 3-hydroxy-, 3-mercapto-, and 3-chlorophenanthro[**9, 10-*e***]1,2,4-triazines (**1a–1c**) were prepared by *v. Laakso et al.* [2]. Although the chemical behaviour of the uncondensed analogues has been extensively studied [3], the reactivity of such condensed systems is not clearly investigated.

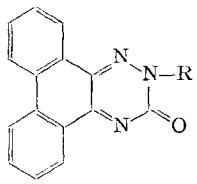
We have found that **1a** is easily N-alkylated when its alkaline solution is treated with dimethyl sulfate or ethyl iodide to give the 2-methyl and the 2-ethyl derivatives **2a** and **2b** respectively. The proposed structures of **2a** and **2b** are supported by the analytical data, and the IR. spectrum of **2a** which showed a strong band at 1670 cm^{-1} characteristic of a ring C=O group meaning that the possible **1d** and **1e** are not formed. Furthermore, **2a** was also obtained *via* the action of diazomethane on **1a**.

The trials to obtain **1b** according to the previously reported methods for the synthesis of triazine derivatives [4] [5] were unsuccessful. It was found that the product previously reported in 1951 as 3-mercapto-phenanthro[**9, 10-*e***]1,2,4-triazine (**1b**) [4] is phenanthroquinone monothiosemicarbazone (**4**), identified by the analytical data, m.p., and mixed m.p.. By refluxing **4** in aqueous potassium hydroxide, compound **1b**, evidenced by the analytical and IR. data, was produced in good yield.

In contrast with the behaviour of **1a** towards alkylating agents resulting in N-alkyl derivatives, the action of the corresponding alkylating agents on **1b** produced, in good yield, the S-alkyl derivatives **1f–1i**, whose structures were evidenced by the analytical data and IR. spectra. Compounds of type **3** (corresponding to **2**) were not isolated. Moreover, compound **1f** was prepared *via* the condensation of phenanthraquinone and S-methylisothiosemicarbazide followed by cyclization of the obtained monoisothiosemicarbazone. Also, **1f** was obtained in good yield by the action of

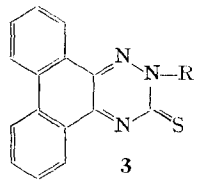


1a Alkylation →



1a X = OH
b X = SH
c X = Cl
d X = OCH_3
e X = OC_2H_5
f X = SCH_3
g X = SC_2H_5
h X = $S-CH_2C_6H_5$
i X = $S-C_6H_3(NO_2)_2(2,4)$
j X = NHC_6H_5
k X = $NHCH_2C_6H_5$
l X = $NHC_6H_4CH_3$-*p*
m X = $NHC_6H_4OCH_3$-*p*
n X = piperidino
o X = morpholino

2a R = CH_3
b R = C_2H_5



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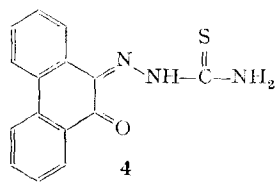

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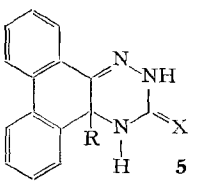
diazomethane on **1b**. Furthermore, when **1f** was hydrolysed by refluxing in alcoholic hydrochloric acid, **1a** was obtained together with methyl mercaptan.

The behaviour of the triazines **1a–1b** towards the action of *Grignard* reagents seemed interesting. Thus, when **1a** and **1b** were treated with alkyl- and aralkyl-magnesium halides, the corresponding 3-hydroxy-, and 3-mercapto-5-alkyl(aralkyl)-phenanthro[9, 10-*e*]2,3,4,5-tetrahydro-1,2,4-triazines **5a–5f** were obtained. The structure of the *Grignard* products are inferred from the analytical data and the IR. spectra. Compounds **5a–5c** showed strong bands at 1620 cm^{-1} (>C=N), 1680–1700 cm^{-1} (>C=O), and 3060–3220 cm^{-1} (>NH). Compounds **5d–5f** showed also strong absorption bands characteristic to >C=N and >NH groups (similar bands were

1a–1b RMgX → Hydrolysis



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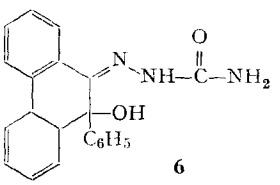

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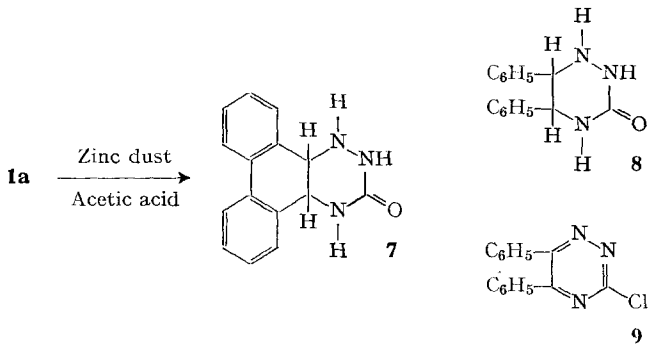
5a X = O; R = CH_3
b X = O; R = C_2H_5
c X = O; R = $CH_2C_6H_5$
d X = S; R = CH_3
5e X = S; R = C_2H_5
f X = S; R = $CH_2C_6H_5$
g X = O; R = C_6H_5

reported for **5g** which was obtained by *Awad et al.* [6] by cyclization of the semicarbzone **6**). The proposed structure was further supported by the NMR. spectrum of **5b** which showed (*t*) 3 H at $\delta = 0.9$ ppm, and a (*q*) 2 H at $\delta = 1.5$ ppm assignable for C_2H_5 group; also (*m*) 9 H at $\delta = 7.3$–8.1 ppm representing 8 aromatic protons and the N(4) hydrogen proton; and (*s*) 1 H at $\delta = 10.36$ ppm indicating another N(2) hydrogen proton (*cf.* the 2,3,4,5-tetrahydro-1,2,4-triazines [7] [8]).

By refluxing **5f** with acetic anhydride, it was converted into **5c**; this conversion propably involves the formation of the intermediate thioacetic acid ester of **5f** followed by hydrolysis [9].

The previous findings showed that the behaviour of the condensed 1,2,4-triazines **1a** and **1b** towards *Grignard* reagents is similar to that of the uncondensed triazines [7] [8]. On the other hand, the reduction of compound **1a** by the action of zinc dust and acetic acid or *p*-thiocresol yielded the hexahydrotriazine derivative **7**. This behaviour is in contrast to the behaviour of the uncondensed analogues which yielded the tetrahydro derivatives [7] [9]. The hexahydrotriazine derivative **7** had the correct analytical data and IR. spectrum. Its NMR. spectrum showed the following signals: (*s*) 2 H at $\delta = 5.6$ ppm assignable to protons at C(5) and C(6); (*m*) 10 H at $\delta = 7.5$–8.8 ppm assignable to 8 aromatic protons and protons at N(1) and N(4); and (*s*) 1 H at $\delta = 11.2$ ppm assignable for one hydrogen proton at N(2). These signals are analogous to those reported for 3-oxo-1,2,3,4,5,6-hexahydro-1,2,4-triazine (**8**) [10]. It is obvious that the hexahydro structure is sterically the more favoured form due to the reduction of the condensed triazine systems, while the tetrahydro structure is the more stable form in case of the uncondensed systems [7] [9].



By reaction with primary and secondary amines, 3-chloro-phenanthro[9,10-*e*]-1,2,4-triazine (**1c**) yielded the corresponding 3-amino derivatives **1j-1o**. Due to the increase of the aromaticity of this condensed 1,2,4-triazine **1c**, the formation of the 3-amino derivatives necessitates longer heating and a higher temperature than in case of the uncondensed analogue 3-chloro-5,6-diphenyl-1,2,4-triazine (**9**) [11].

Experimental

All m.p.'s are uncorrected. The IR. spectra were recorded on an Infrared Spectrophotometer *Unicam* SP 200G. The NMR. spectra were measured at 60 MHz in $(CH_3)_2SO$ solution with tetramethylsilane as internal standard.

Phenanthroquinone monothiosemicarbazone (**4**). A solution of phenanthroquinone (2.0 g) and thiosemicarbazide (0.9 g) in acetic acid (25 ml), was refluxed for 5 min, whereby a precipitate began to separate. After cooling the precipitate was filtered off and crystallized from acetic acid: Yellow needles; m.p. 216° (dec.), yield 67%.

$C_{15}H_{11}N_3OS$ Calc. C 67.97 H 4.17 N 15.83 S 12.08%
Found ,, 68.04 ,, 4.11 ,, 15.80 ,, 12.06%

3-Mercapto-phenanthro[9,10-e]1,2,4-triazine (**1b**). A solution of compound **4** (2.0 g) in 5% aqueous potassium hydroxide (100 ml) was refluxed for 30 min, filtered, cooled, then acidified with dilute hydrochloric acid. The solid separated was collected, washed with water, and crystallized from chlorobenzene: Red needles; m.p. 275° (dec.), yield 92%.

$C_{15}H_9N_3S$ Calc. C 68.42 H 3.44 N 15.95 S 12.16%
Found ,, 68.72 ,, 3.61 ,, 15.82 ,, 12.23%

Compound **2a** *by action of dimethylsulfate on* **1a**. Dimethyl sulfate (2 mmol) was added to a solution of compound **1a** (2 mmol) in 5% aqueous potassium hydroxide (25 ml). The mixture was shaken for 10 min then left for 2 h, the precipitate formed was filtered, washed with water, and crystallized from ethanol: Yellow crystals; m.p. 223°, yield 88%.

$C_{16}H_{11}N_3O$ Calc. C 73.54 H 4.24 N 16.08% Found C 73.11 H 4.56 N 15.96%

Compound **2b** *by the action of ethyl iodide on* **1a**. The mixture of ethyl iodide (2 mmol) and of a solution of compound **1a** (2 mmol) in 5% aqueous potassium hydroxide (25 ml) was shaken for about 15 min and left overnight at room temperature. The precipitate formed was filtered, washed with water, and crystallized from aqueous ethanol (50%): Yellow needles; m.p. 178–179°, yield 60%.

$C_{17}H_{13}N_3O$ Calc. C 74.01 H 4.76 N 15.26% Found C 73.88 H 4.64 N 15.11%

Compounds **1f–1i** *by action of dimethyl sulfate or alkyl halides on* **1b** (*Table 1*). The previous methods were followed for their preparation. The obtained yellow products were crystallised from acetic acid except compound **1f** which was crystallized from dilute pyridine.

Table 1. *3-S-Alkyl-phenanthro[9,10-e]1,2,4-triazines* **1f–1i**

Compound	Alkylating agent	M.P. °C	Yield %	Formula	Analysis %	C	H	N	S
1f	Dimethyl sulfate	158	62	$C_{16}H_{11}N_3S$	Calc.	69.29	3.99	15.15	11.55
					Found	69.40	4.08	14.94	11.70
1g	Ethyl iodide	135	45	$C_{17}H_{13}N_3S$	Calc.	70.08	4.50	14.42	11.00
					Found	70.48	4.41	14.65	11.61
1h	Benzyl chloride	185	37	$C_{22}H_{15}N_3S$	Calc.	74.76	4.27	11.88	9.07
					Found	74.06	4.66	12.01	9.36
1i	2,4-Dinitro-chlorobenzene	223	25	$C_{21}H_{11}N_5O_4S$	Calc.	58.73	2.59	16.03	7.46
					Found	58.78	2.81	15.69	8.02

Action of diazomethane on **1a–1b**. An ethereal solution of diazomethane (prepared from 7.0 g nitrosomethylurea) was added to 1.0 g of each of **1a** and **1b**. After standing overnight at about 0°, the solution was evaporated at room temperature, whereby a precipitate of **2a** and **1f** was formed respectively; identified by m.p.'s and mixed m.p.'s with samples prepared by action of dimethylsulfate.

Phenanthroquinone mono-S-methylisothiosemicarbazone. A solution of phenanthroquinone (0.4 g) and S-methylisothiosemicarbazide hydrochloride (0.4 g) in glacial acetic acid (10 ml) was boiled for 5 min. After cooling, the precipitate formed was filtered off, washed with cold water and crystallized from acetic acid: Orange yellow needles; m.p. 240°.

Compound **1f** *by cyclisation of phenanthroquinone mono-S-methylisothiosemicarbazone.* The semicarbazone (0.3 g) was refluxed for 15 min in 5% aqueous potassium hydroxide (15 ml). After cooling, the precipitate formed was filtered, washed with water, and crystallized from pyridine: Yellow needles; identified as **1f** by m.p. and mixed m.p.

Compound **1a** *by action of ethanolic hydrochloric acid on* **1f**. Compound **1f** (0.2 g) was refluxed in 3N ethanolic hydrochloric acid. The smell of the evolved methylmercaptan was distinctly noticed. After 7 h the smell nearly disappeared and a precipitate began to appear. After cooling, the precipitate was filtered, washed with cold ethanol, then crystallized from pyridine: Yellow crystals; identified as **1a** by m.p. and mixed m.p.

Compounds **5a–5f** *by action of organomagnesium halides on* **1a–1b** (*Table 2*). To a *Grignard* solution (prepared from 2.0 g magnesium and the corresponding halide), a suspension of 2.0 g of each of **1a** and **1b** in dry benzene was added gradually. The mixture was refluxed for 2 h, then kept overnight at room temperature. The complex was then decomposed using a cold saturated aqueous solution of ammonium chloride. The organic layer was separated, dried, and evaporated at room temperature. The colourless products were crystallized from the appropriate solvent.

Table 2. *Compounds* **5a–5f** *from* **1a** *and* **1b** *by* Grignard *reagents*

From	Compound	R	M.P. °C	Solvent of cryst.	Yield %	Formula	Analysis %	C	H	N	S
1a	**5a**	CH_3	268	Chlorobenzene	80	$C_{16}H_{13}N_3O$	Calc.	72.92	5.53	15.99	
							Found	73.41	5.60	15.71	
1a	**5b**	C_2H_5	255	dil. pyridine	55	$C_{17}H_{15}N_3O$	Calc.	73.54	5.45	15.14	
							Found	73.92	5.51	15.00	
1a	**5c**	$CH_2C_6H_5$	233	Benzene	70	$C_{22}H_{17}N_3O$	Calc.	77.77	5.04	12.38	
							Found	78.03	5.00	12.10	
1b	**5d**	CH_3	244	Chlorobenzene	38	$C_{16}H_{13}N_3S$	Calc.	68.79	4.59	15.04	11.47
							Found	68.34	4.81	15.53	11.12
1b	**5e**	C_2H_5	230	Ethanol	85	$C_{17}H_{15}N_3S$	Calc.	69.55	5.15	14.32	10.93
							Found	69.70	5.32	14.31	10.55
1b	**5f**	$CH_2C_6H_5$	245	Chlorobenzene	85	$C_{22}H_{17}N_3S$	Calc.	74.33	4.82	11.82	9.02
							Found	74.06	4.66	11.50	8.92

Action of acetic anhydride on **5f**. Compound **5f** (0.5 g) was refluxed in acetic anhydride (15 ml) for 20 h, then charcoal (0.2 g) and water (5 ml) were added. The mixture was again refluxed for one hour, filtered while hot, then cooled, poured onto cold water (*ca.* 100 ml), and left overnight. The precipitate formed was filtered off and crystallized from benzene: Colourless crystals of **5c** identified by m.p. and mixed m.p.

Compound **7** *by reduction of* **1a**. – (*a*) *By zinc dust and acetic acid.* To a suspension of compound **1a** (0.5 g) in acetic acid (60 ml) and ethanol (10 ml) zinc dust (0.3 g) was added. The mixture was refluxed for 2 h. The clear solution was filtered while hot, evaporated till nearly half of its volume, cooled and poured onto cold water (*ca.* 100 ml). The precipitate formed was filtered off, washed with cold water, and crystallized from pyridine: Colourless crystals of compound **7**; m.p. 319°, yield 93%.

$C_{15}H_{13}N_3O$ Calc. C 71.69 H 5.21 N 16.72% Found C 71.99 H 5.72 N 16.41%

(*b*) *By p-thiocresol.* Compound **1a** (1.0 g) was heated in an oil bath for 5 h at 180–190° with *p*-thiocresol (2.0 g). The mixture was then cooled, washed with hot petroleum ether (b.p. 60–80°), and crystallized from pyridine: Colourless crystals; m.p. 319° (dec.), yield 96%; identified as **7** by m.p. and mixed m.p. with a sample prepared according to method (a).

Compounds **1j–1o** *by action of amines on* **1c** (*Table 3*). A mixture of **1c** (0.5 g) and the appropriate amine (1–2 g) was heated (or refluxed) for 10 h, then cooled. The solid obtained was washed with ethanol and crystallized from dimethyl formamide. The products are sparingly soluble in ethanol, but soluble in pyridine.

Table 3. *3-Amino-phenanthro[9,10-e]1,2,4-triazines* (**1j–1o**)

Comp.	Amine	M.P. °C	Colour	Yield %	Formula	Analysis %	C	H	N
1j	Aniline	320	Orange-yellow	70	$C_{21}H_{14}N_4$	Calc.	78.19	4.37	17.37
						Found	78.70	4.87	17.01
1k	Benzylamine	236	Orange-yellow	53	$C_{22}H_{16}N_4$	Calc.	78.55	4.81	16.68
						Found	78.92	4.80	16.40
1l	*p*-Toluidine	317	Brown	80	$C_{22}H_{16}N_4$	Calc.	78.55	4.81	16.68
						Found	77.98	4.30	16.42
1m	*p*-Methoxy-aniline	301	Red	77	$C_{22}H_{16}N_4O$	Calc.	74.98	4.57	15.92
						Found	74.60	4.45	15.91
1n	Piperidine	205	Brown	58	$C_{20}H_{18}N_4$	Calc.	76.36	5.77	17.84
						Found	76.11	5.29	17.31
1o	Morpholine	171	Brown	67	$C_{19}H_{16}N_4O$	Calc.	72.06	5.08	17.69
						Found	71.98	5.18	17.60

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