

**REACTION OF THIOAMIDES
WITH 2,3-DICHLORO-1,4-NAPHTHOQUINONE.
A NOVEL SYNTHESIS OF NAPHTHO[2,3-*d*]THIAZOLE-4,9-DIONES***

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The reaction of thioamide *II* with 2,3-dichloro-1,4-naphthoquinone (*I*) in ethanol gave naphtho[2,3-*d*]thiazole-4,9-diones (*IV*). The intermediates, 2-thioamido-3-chloro-1,4-naphthoquinones *III* were also isolated from the reaction medium and could be separately transformed to *IV* by further boiling in aqueous ethanol containing bicarbonate. The reaction of thiosemicarbazide with *I* under similar conditions gave naphtho[2,3-*e*]-2-amino-4*H*-1,3,4-thiadiazine-5,10-dione (*VII*).

Interest in the chemistry of thiazoles and their derivatives has increased since the discovery of a simple thiazole ring in vitamin B₁ and a thiazolidine ring in penicillins. Numerous reports appeared in literature ascribing antimicrobial^{1,2}, antiradiation^{3,4} and antiparasitic⁵ properties of this heterocyclic ring. The recent discovery that quinones are also endowed with antimalarial⁶, antiprotozoal⁷ and antitumour⁸ properties has directed the attention to the synthesis of fused thiazolo quinone ring system with the hope that a combination of the favourable properties of both the quinone and the thiazole may be achieved. The present article deals with a novel synthesis of naphthothiazole diones.

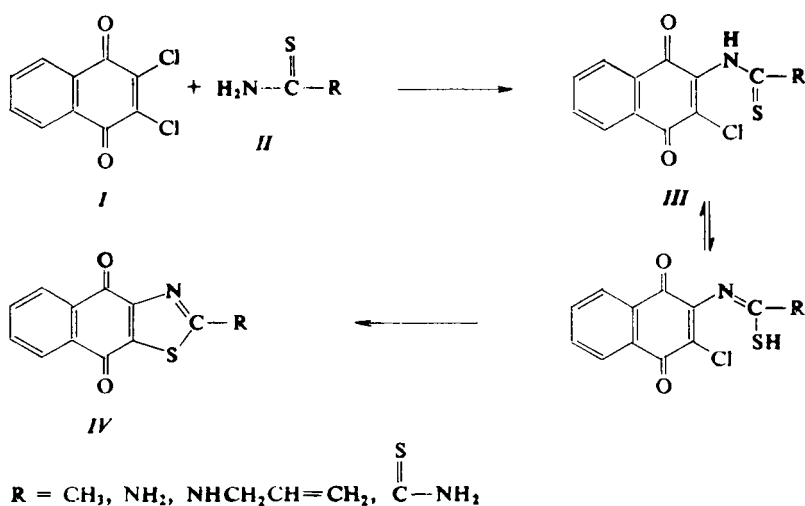
Heating equimolar amounts of 2,3-dichloro-1,4-naphthoquinone (*I*) and thioamides *II* in ethanol or a dioxan-ethanol mixture resulted in reddish brown to violet solutions that gradually precipitated dark red to violet crystalline solids under refluxing conditions. The formation of solids was enhanced by addition of aqueous solution of sodium hydrogen carbonate to the refluxing mixture. Elemental analyses showed the absence of halogen in these compounds and the involvement of only one molecule of the thioamide in their formation. Warming the compounds in concentrated sulphuric acid, gave yellow to brownish solutions from which they were precipitated on dilution without eliminating the thioamide moiety suggesting the incorporation of the latter in a stable cyclic structure. The compounds retained their quinonoid nature as indicated from the discharge of their colours on treatment

* Part XIII in the series Heterocyclic Quinones.

with stannous chlorido-acetic acid and their ready oxidation to the original colours on exposure to air. Moreover, the IR spectra have consistently shown bands in the range 1 670–1 663, 1 650–1 635 and 1 610–1 600 cm^{-1} characteristic of $\nu(\text{C}=\text{O})$, $\nu(\text{polarised C}=\text{O})$ and $\nu(\text{C}=\text{C})$ conjugated with $\text{C}=\text{O}$ in quinones, respectively.

The above characteristics of these compounds are apparently consistent with a naphthothiazoledione structure *IV*. The structure assignment of diones (*IV*) was confirmed by preparing 2-methylnaphtho[2,3-*d*]thiazole-4,9-dione (*IV*, $\text{R} = \text{CH}_3$) by a method of Boggust and coworkers⁹ through the interaction of 2-amino-3-mercapto-1,4-naphthoquinone with acetaldehyde and showing that it is identical with the product obtained from the interaction of *I* with thioacetamide.

In the mechanism of formation of *IV* (Scheme 1) it is assumed that the thioamide *II* undergoes a nucleophilic displacement of one chlorine atom in *I* to give 2-thioamido-3-chloro-1,4-naphthoquinone *III*, which on losing a hydrogen chloride molecule

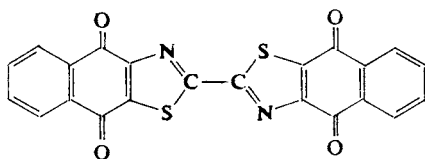


SCHEME 1

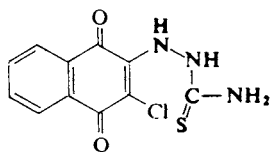
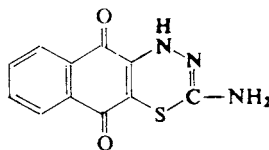
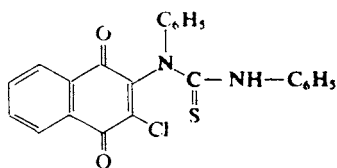
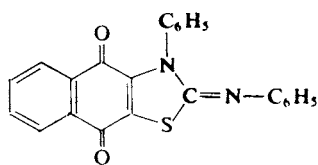
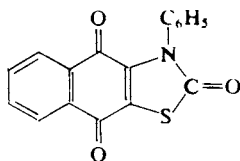
gives *IV*. The involvement of *III* as intermediates was indicated from the isolation of *III* from the reaction medium and their ready transformation to *IV* by further refluxing in aqueous ethanolic sodium hydrogen carbonate solution. Moreover, on conducting the reaction between *I* and thioamide in a weakly polar solvent such as dioxan for a limited period (10–20 min), compounds *III* only resulted. These on boiling in a polar solvent in presence or absence of hydrogen carbonate gave *IV*. The intermediates *III* are characterised by lighter colours and by ease solubility in most of organic solvents. Their IR spectra exhibited medium to strong bands in the ranges 3 420–3 260, 1 140–1 125 and 770–725 cm^{-1} characteristic of $\nu(\text{NH})$, $\nu(\text{C}=\text{S})$ and $\nu(\text{C}-\text{Cl})$, respectively.

Dithioamide, having two functional thioamide groups could condense with two moles of *I* to give a bis-naphtho[2,3-*d*]thiazole-4,9-dione (*V*) which was also ob-

tained by treating *IV*, $R = \overset{\text{S}}{\underset{\parallel}{\text{C}}}-\text{NH}_2$, with a further mole of *I*.

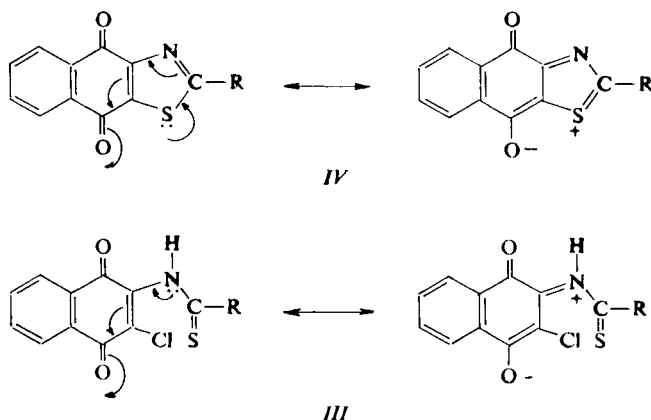
*V*

Further, reaction between *I* and thiosemicarbazide in molar ratios gave a brownish violet product containing no halogen and highly stable in sulphuric acid suggesting the involvement of the thiosemicarbazide moiety in a heterocyclic form. The compound was assigned by analogy as naphtho[2-3, *e*]2-amino-4*H*-1,3,4-thiadiazine-5,10-dione (*VII*) apparently formed through the intermediate *VI*, which was also isolated from the same reaction mixture.

*VI**VII**VIII**IX**X*

The reaction of *I* with *N,N'*-diphenylthiourea as a secondary thioamide proceeded also readily to give a violet coloured naphtho[2,3-*d*]-3-phenylthiazoline-2-anil-4,9-dione (*IX*) possibly formed by a similar mechanism and involving *VIII* as an intermediate. Compound *IX* could be partially hydrolysed by acid in an aqueous alcoholic solution¹⁰ to give a yellow coloured naphtho[2,3-*d*]-3-phenylthiazoline-2,4,9-trione (*X*). The latter gave back the violet product *IX* on refluxing with aniline in ethanol.

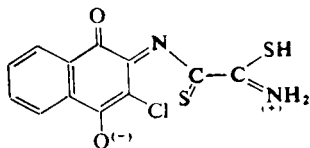
The UV-visible spectra of the heterocyclic compounds *IV*, *VII* and *IX* show a common pattern of absorption comprising at least 4 bands in the UV-side and one band in the visible side. Of interest is the band located in the visible region which by analogy to previous spectral studies on heterocyclic quinones¹¹⁻¹⁴, is ascribed to charge transfer (C.T.) from the heteroatom(s) of the heterocycle into the quinone ring, Scheme 2. This band exhibits remarkable variation both in position and inten-



SCHEME 2

sity depending on the electronic state of the substituent *R* (Table I), from which it is deduced that in compounds *IV* a more electron releasing substituent causes a red shift of the band. The spectra of the noncyclic products *III* show the same pattern of absorption like *IV* but with variation in band position and intensity. The most noticeable of these variations is the remarkable blue shift of the C.T. band as compared with that in the spectra of *IV*. This is readily explainable on basis of the structures assigned to the noncyclic compounds *III* having the thioamide substituent linked to the quinone ring through a nitrogen atom. A C.T. originating from a nitrogen atom in these compounds will be less easier than C.T. originating from a more electron releasing sulfur atom in the cyclic compounds *IV*; an easier electronic delocalisation from sulfur will accordingly cause a redder shift of the C.T. band, Scheme 2.

As exceptional case was the C.T. band of the noncyclic intermediate *III*, $R = -CS-NH_2$ obtained from dithiooxamide which was red shifted than that of the cyclic product *IV*, $R = -CS-NH_2$). This can be explained if the formation of the excited form *XI* is possible from *III*, $R = -CS-NH_2$ by rearrangement which will

*XI*

contribute more to C.T. than the cyclic product. The spectrum of compound *X* prepared by hydrolysis of *IX* has shown its C.T. band remarkably blue shifted (~ 85 nm) from that of the original compound *IX*. This is attributed to the strong antagonising C.T. interaction of the carbonyl group in the 2 position of the thiazoline ring which minimises C.T. from sulfur to the quinone ring.

EXPERIMENTAL

All the melting points determined are uncorrected. The UV-visible spectra were measured in ethanol using a Pye Unicam SP 8000 UV recording spectrophotometer. The IR spectra were measured using KBr discs in a Unicam SP 200 G IR spectrophotometer.

Naphtho[2,3-*d*]thiazole-4,9-diones *IV* and 2-Thioamido-3-chloro-1,4-naphthoquinones *III*

A solution of 2,3-dichloro-1,4-naphthoquinone (*I*) (2.27 g, 10 mmol) in the minimum volume of dioxan was treated with 10 mmol of the thioamide *II* in ethanol. The mixture was boiled until a brownish red to violet colour is obtained and a dark solid started to precipitate (20–30 min). Ethanol (20 ml) together with a few milliliters of 10% $NaHCO_3$ are added and reflux was continued (1–2 h) until precipitation of the dark solid is complete. The solid is filtered and recrystallised from the proper solvent. The compounds are given in Tables I and II. The mother liquor after filtering off the solid *IV* was diluted with water whereby light brown to reddish precipitates of *III* separated out. These were collected, dried at $80^\circ C$ and crystallised from toluene or toluene–light petroleum. The compounds are included in Tables I and II.

The reactions of *I* with thioamides *II* in dioxane only for a short period (15–20 min) gave reddish brown solutions which on dilution with water precipitated only the intermediates *III*. Refluxing *III* in aqueous ethanolic sodium hydrogen carbonate solution gave *IV*.

Bis-naphtho[2,3-*d*]thiazole-4,9-dione (*V*)

A mixture of 2-thioamidonaphtho[2,3-*d*]thiazolo-4,9-dione, (1.37 g, 5 mmol) and *I* (1.135 g, 5 mmol) was refluxed in ethanol–dioxane mixture (30 ml) containing 5 ml of 10% aqueous sodium hydrogen carbonate for 2 h. The resulting deep violet solution precipitated on cooling a dark solid crystallised from dioxane as crimson red needles of *V*, m.p. $304-306^\circ C$. The characteristics of the compound are included in Tables I and II.

Refluxing 2 mol of *I* with 1 mol of dithiooxamide (*II*, $R = -CS-NH_2$) in aqueous ethanolic sodium hydrogen carbonate solution for 2 h gave also *V*, m.p. and mixed m.p. $304^\circ C$.

Naphtho[2,3-*d*]-3-phenylthiazoline-2-anil-4,9-dione (*IX*)

A mixture of *I* (2.27 g, 10 mmol) and *N,N'*-diphenylthiourea (2.28 g, 10 mmol) was refluxed in ethanol (50 ml) for 30 min during which a deep reddish violet solution developed and a reddish violet solid started to separate out. 5 ml of 10% sodium hydrogen carbonate was then added and the reflux was continued for a further 1 h. The precipitated solid was collected, washed with ethanol, water and finally with ethanol. Yield, 2.9 g (76%). Recrystallisation from dioxan gave violet red needles of *VII*, m.p. 264–266°C. For $C_{23}H_{14}N_2O_2S$ (402.4) calculated: 72.25% C, 3.66% H, 7.33% N, 8.38% S; found: 72.37% C, 3.58% H, 7.15% N, 8.51% S. IR spectrum (cm^{-1}): 1 670^s (C=O), 1 635 (polarised (C=O)), 1 610 (C=C conjugated with C=O), 1 490 (C=N) and 760, 710 (5 adjacent aromatic H).

TABLE I

Reaction products of thioamides with 2,3-dichloro-1,4-naphthoquinone

No	Product	Thioamide	M.P., °C (yield, %)	Solvent	Colour of crystals
1	<i>IV</i> R = CH ₃	thioacetamide	318–320 (85)	toluene	violet
2	<i>III</i> R = CH ₃	thiacetamide	145 ^a (—)	toluene– –light petroleum	light brown
3	<i>IV</i> R = NH ₂	thiourea	333 (62)	dioxane	violet
4	acetate	—	318–319 (—)	dioxane	greenish brown
5	<i>p</i> -nitrobenzylidene derivative	—	350 (—)	dioxane–ethanol	brown
6	<i>III</i> R = NH ₂	thiourea	175 (—)	toluene– –light petroleum	reddish brown
7	<i>IV</i> R = NHCH ₂ CH=CH ₂	allylthiourea	315–317 (70)	dioxane	reddish violet
8	<i>III</i> R = NHCH ₂ CH=CH ₂	allylthiourea	156 (—)	toluene	light brown
9	<i>IV</i> R = CS–NH ₂	dithiooxamide	350 (80)	dioxane	reddish violet
10	<i>III</i> R = CS–NH ₂	dithiooxamide	260 (—)	toluene	brown
11	<i>V</i>	dithiooxamide	304–306 (86)	dioxane	red

^a Decomposition at 115°C.

The mother liquor was diluted with water whereby a reddish orange precipitate of 2-diphenylthiocarbamido-3-chloro-1,4-naphthoquinone was obtained, crystallised from benzene as brown crystals, m.p. 138–140°C. For $C_{23}H_{15}ClN_2O_2S$ (438.8) calculated: 65.95% C, 3.58% H, 8.48% Cl, 6.69% N, 7.65% S; found: 66.10% C, 3.62% H, 8.30% Cl, 6.65% N, 7.70% S. IR spectrum (cm^{-1}): 3 320 (NH), 1 135 (C=S), 760 (C—Cl).

Naphtho[2,3-*d*]-3-phenylthiazoline-2,4,9-trione (*X*)

1 g of *IX* was suspended in 50 ml ethanol, and treated with 50 ml of 40% sulphuric acid (v/v). The mixture was refluxed until *IX* dissolved giving a yellow solution (2 h) then for a further 1 h,

TABLE II
Elemental analyses and spectral data

No	Formula (m.w.)	Calculated/Found					IR, cm^{-1}	UV-VIS ^a (λ , nm)
		% C	% H	% N	% S	% Cl		
1	$C_{12}H_7NO_2S$ (229.26)	62.88	3.06	6.11	13.97	—	1 665 ^b , 1 650 ^c , 1 605 ^d	490 (2 800)
		62.62	3.15	6.25	13.70	—		
2	$C_{12}H_8ClNO_2S$ (265.72)	54.24	3.01	5.27	12.05	13.37	3 420 ^e , 1 670 ^b , 1 130 ^f 765 ^g	468 (2 150)
		54.35	2.92	5.15	12.18	13.58		
3	$C_{11}H_6N_2O_2S$ (230.25)	57.39	2.61	12.17	13.91	—	3 320 ^e , 3 290 ^h , 1 663 ^b 1 648 ^c , 1 660 ^d	500 (1 900)
		57.58	2.75	12.00	14.15	—		
4	$C_{13}H_8N_2O_4S$ (288.28)	—	—	9.72	11.11	—	1 750 ⁱ , 1 670 ^b	470 (1 350)
		—	—	9.91	11.28	—		
5	$C_{18}H_9N_3O_4S$ (363.35)	—	—	11.57	8.82	—	1 520 ^j , 1 340 ^k	— (—)
		—	—	11.84	9.01	—		
6	$C_{11}H_7ClN_2O_2S$ (266.71)	49.53	2.63	10.51	12.01	13.32	3 440 ^e , 3 340 ^h , 1 680 ^b 1 125 ^f , 765 ^g	474 (1 400)
		49.34	2.55	10.60	12.35	13.81		
7	$C_{14}H_{10}N_2O_2S$ (270.31)	62.22	3.70	10.37	—	—	1 660 ^b , 1 645 ^c , 1 605 ^d	485 (2 250)
		62.18	3.83	10.45	—	—		
8	$C_{14}H_{11}N_2O_2S$ (271.32)	54.81	3.59	9.14	—	11.58	3 325 ^h , 1 660 ^b , 1 140 ^f 765 ^g	470 (1 650)
		54.80	3.67	9.41	—	11.50		
9	$C_{12}H_6N_2O_2S_2$ (274.32)	52.55	2.19	10.22	—	—	1 670 ^b , 1 650 ^c	490 (3 200)
		52.65	2.05	10.36	—	—		
10	$C_{12}H_7ClN_2O_2S_2$ (310.78)	45.79	2.23	10.17	—	11.29	3 430 ^e , 3 320 ^h , 1 667 ^b 1 137 ^f , 770 ^g	— (—)
		45.92	2.40	10.30	—	11.44		
11	$C_{22}H_8N_2O_2S_2$ (396.45)	66.97	2.02	7.07	—	—	1 663 ^b , 1 645 ^c , 1 605 ^d	— (—)
		67.24	2.10	7.25	—	—		

^a In ethanol; ^b (C=O); ^c (C=O) polarized; ^d (C=O) conjugated with C=C in quinones; ^e (NH) primary; ^f (C=S); ^g (C—Cl); ^h (NH) secondary; ⁱ (C=O) in acetyl; ^j (NO₂) asym.; ^k (NO₂) sym.

cooled and diluted with an equal volume of water when unchanged *IX* precipitated which was filtered off (0.35 g). The filtrate was extracted with chloroform. The chloroform extract was concentrated to near dryness precipitating a yellow product which was crystallised from excess methanol as yellow platelets of *X* m.p. 215°C. For $C_{17}H_9NOS$ (275.3) calculated: 66.45% C, 2.93% H, 10.42% S; found: 66.60% C, 3.30% H, 4.62% N, 10.30% S. IR spectrum (cm^{-1}): 1 690, 1 675, 1 665 (C=O), 740, 710 (5 adjacent aromatic H).

Reaction of *X* with Aniline

A mixture of 0.2 g of *X* and 0.5 ml of aniline was refluxed with 20 ml of ethanol and 2 g of anhydrous zinc chloride for about 1/2 h when it darkened and a violet crystalline product precipitated. The solid was filtered (0.17 g) and crystallised from dioxane as violet needles m.p. 266°C undepressed on admixture with a sample of *IX* obtained from *I* and *N,N'*-diphenylthiourea. The two compounds showed identical IR and UV-visible spectra.

Naphtho[2,3-*e*]-2-amino-4*H*-1,3,4-thiadiazine-5,10-dione (*VII*) and 2-Thiosemicarbazido-3-chloro-1,4-naphthoquinone (*VI*)

A mixture of *I* (2.27 g, 10 mmol) and thiosemicarbazido (0.91 g, 10 mmol) was refluxed in ethanol (100 ml) for about 15 min when a red solution resulted and a dark solid started to separate. Reflux was continued for further 10 min. The precipitated solid was filtered from the hot reaction mixture, yield, 1.3 g. The mother filtrate was cooled, diluted with water and the precipitated orange red solid was collected. The first solid (*VII*) was crystallised from excess dioxane, m.p. 180°C. For $C_{11}H_7N_3O_2S$ (245.2) calculated: 53.88% C, 2.88% H, 17.14% N, 13.06% S; found: 53.71% C, 2.96% H, 17.17% N, 13.25% S. IR spectrum (cm^{-1}): 3 400–3 200 (NH), 1 670 (C=O) of quinones), 780 (4 adjacent aromatic H). UV visible spectrum (ethanol): λ_{max} 495 nm (ϵ 3 228).

The solid from mother liquor was crystallised from toluene–light petroleum as orange brown crystals of *VI*, m.p. 262°C. For $C_{11}H_8ClN_3O_2S$ (281.7) calculated: 46.89% C, 2.84% H, 12.61% Cl, 14.92% N, 11.37% S; found: 46.70% C, 2.90% H, 12.50% Cl, 14.78% N, 11.22% S.

2-Methylnaphtho[2,3-*d*]thiazole-4,9-dione (*IV*, R = CH₃) by a Procedure of Boggust and coworkers⁹

A suspension of 5 g of *I* in 50 ml ethanol was treated with excess ammonia (10 ml) refluxed for 1 h. The resulting yellow-orange solution was concentrated to half of its volume, cooled and the precipitated orange solid (3.4 g) was crystallised from ethanol as needles of 2-amino-3-chloro-1,4-naphthoquinone, m.p. 182–184°C. For $C_{10}H_6ClNO_2$ (207.6) calculated: 57.83% C, 2.89% H, 6.75% N; found: 58.05% C, 2.80% H, 6.91% N. UV spectrum (in $CHCl_3$): λ_{max} 430; ϵ_{max} 1 249.

A solution of 2 g of the above amino derivative in ethanol (30 ml) was refluxed with 10 ml of 1% aqueous sodium sulfide solution for 1 h. The resulting blue mixture was acidified with dilute acetic acid and the precipitated red solid was collected (1.6 g) and crystallised from dioxane as orange-red needles of 2-amino-3-mercapto-1,4-naphthoquinone, m.p. 293–295°C. For $C_{10}H_7NOS$ (189.2) calculated: 58.54% C, 3.41% H, 6.83% N, 15.61% S; found: 58.41% C, 3.62% H, 6.92% N, 14.97% S. UV spectrum (in $CHCl_3$): λ_{max} 445 nm, ϵ_{max} 2 843.

1 g of 2-amino-3-mercapto-1,4-naphthoquinone was suspended in 30 ml ethanol and treated with 3 ml acetaldehyde and 5 ml glacial acetic acid. The mixture was refluxed for 1 h and cooled. The precipitated solid was collected (0.68 g) and crystallized from toluene as violet needles of *IV*, R = CH₃, m.p. 319°C undepressed by mixing with a sample obtained by interaction of *I* and thioacetamide. The compounds gave identical UV-visible and IR spectra.

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