Synthesis of Some New Spiro Naphtho[2,3-*d*][1,3]dithiole-4,9-dione Derivatives

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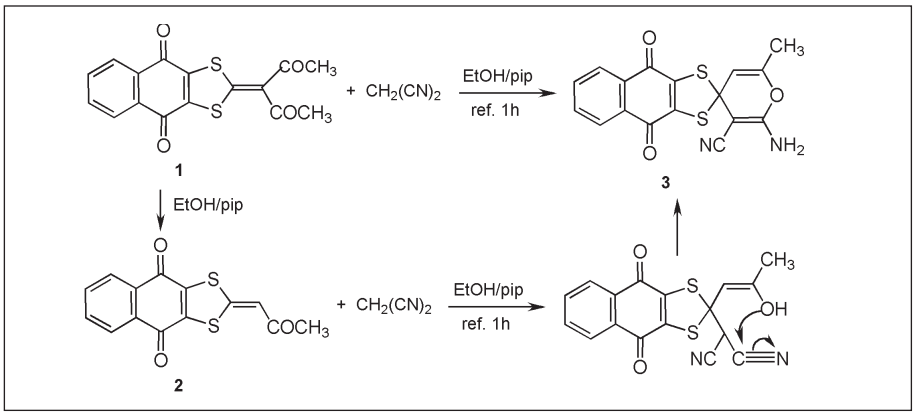

2(1-Acetyl-2-oxopropylidene)naphtho[2,3-*d*][1,3]dithiole-4,9-dione **1** reacts with a variety of bidentates reagents to give some new functionally substituted spiro naphthodithiole-4,9-dione derivatives.

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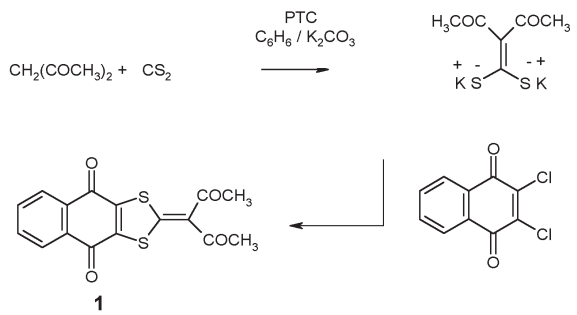
Quinones are widely distributed in nature and play a vital role in certain cellular functions [1-4]. Many drugs used in cancer chemotherapy also contain a quinone group in their structure [5-7].

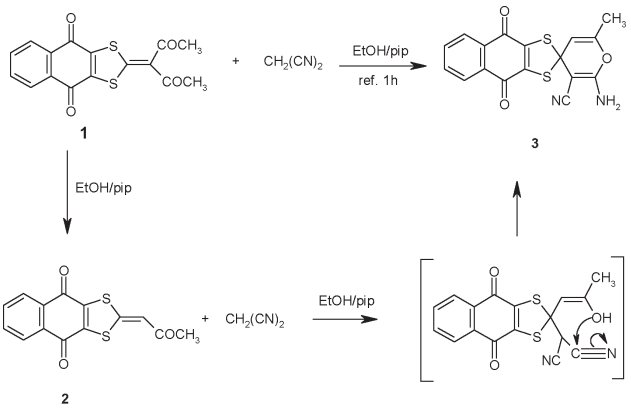
The synthesis of ketoketen [8] or cyanoketene S,S-acetals [9] as well as heterocyclic ketene N,N- [10-15] or N,S-acetals [16-18] has attracted considerable attention as these compounds have been used as versatile starting materials for the synthesis of a wide variety of fused heterocycles. In an extension of our studies [19-22] on the application of cyanoketen, ketoketene, cyanoketoketene S,S- or N,S-acetals in heterocyclic synthesis, we report here the synthesis of some new spiro naphtho[2,3-*d*][1,3]dithiole-4,9-diones using hetero cyclic ketene S,S-acetals **1**.

2-(1-Acetyl-2-oxopropylidene)naphtho[2,3-*d*][1,3]dithiole-4,9-dione **1** was obtained *via* reaction of pentane-2,4-dione, carbon disulphide and 2,3-dichloronaphthoquinone in a one pot reaction using phase transfer catalysis conditions [K_2CO_3/benzene/tetrabutylammonium bromide] (TBAB) in almost 90% yield.



Compound **1** was allowed to react with malononitrile in refluxing aquas ethanol in presence of sodium ethoxide or piperidine where 2'-amino-6'-methyl-4,9-dioxo-4,9-dihydrospiro[naphtha[2,3-*d*][1,3]dithiole-2,4'pyran]-3'carbonitrile **3** was precipitated after heating for 1 hour. This reaction occurred *via* hydrolysis of one of the two acetyl groups of compound **1** followed by a nucleophilic addition of active methylene group of malononitrile to the ethelenic bond of the resultant compound **2** with subsequent cyclization.

This proposed mechanism was confirmed by a two-steps reaction where compound **1** was first deacylated, in boiling aquas ethanol containing piperidine or sodium ethoxide, into the intermediate product 2-(2-oxopropylidene)naphtho[2,3-*d*][1,3]dithiole-4,9-dione **2** which was then reacted with malononitrile in presence of a catalytic amount of piperidine to afford compound **3**. The IR and ^{1}H-nmr data of compound **2** are in accordance with its structure.



On the other hand, when compound **1** was reacted with ethylcyanoacetate under the same experimental conditions (aquas ethanol containing piperidine equivalent) two compounds were obtained. The major one was precipitated on heating and proved to be ethyl 2'-amino-6'-methyl-4,9-dioxo-4,9-dihydrospiro[naphtho[2,3-*d*][1,3]dithiole-2,4'-pyran]-3'-carboxylate **4**, the other product was separated from the mother liquor and was identified as 2'-hydroxy-6'-methyl-4,9-dioxo-4,9-dihydrospiro[naphtho[2,3-*d*]-[1,3]dithiole-2-4'-pyran]-3'-carbonitrile **5**. The reaction pathway is thus assumed to involve an intramolecular nucleophilic attack of the –OH group of the resultant adducts at either the cyano or ethoxycarbonyl groups of ethylcyanoacetate to give compound **4** or **5**, respectively.

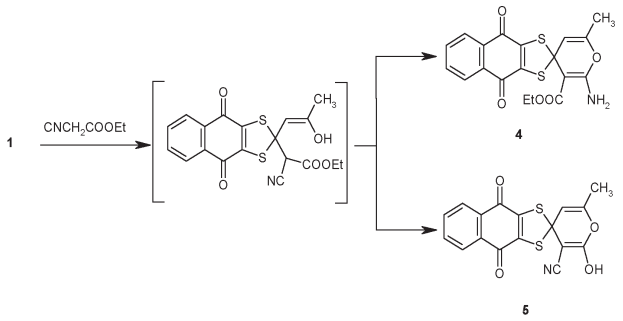


Table 1

Physical and Analytical Data of the Prepared Compounds

Prod. No.	Yield %	M.P.	Mol. Formula (M. Wt.)	C%	H% (Calc. / Found)	N%	S%
1	85	132	$C_{16}H_{10}O_4S_2$	58.17	3.05		19.41
			330.39	58.00	3.30		19.70
2	70	200	$C_{14}H_8O_3S_2$	5832	2.80		22.24
			288.35	58.56	2.60		22.00
3	75	312	$C_{17}H_{10}N_2O_3S_2$	57.61	2.84	7.90	18.10
			354.41	57.42	2.63	7.65	18.32
4	65	155	$C_{19}H_{15}NO_5S_2$	56.84	3.77	3.49	15.97
			401.47	56.60	3.44	3.60	15.70
5	20	235	$C_{17}H_9NO_4S_2$	57.45	2.55	3.94	18.04
			355.40	57.25	2.50	4.15	17.85
6	72	186	$C_{19}H_{14}O_4S_2$	61.60	3.82		17.31
			370.45	61.83	3.95		17.00
7	80	215	$C_{18}H_{12}O_5S_2$	58.05	3.25		17.22
			372.43	58.31	3.01		17.50
8	75	350	$C_{17}H_{12}N_2O_4S_2$	54.83	3.25	7.52	17.22
			372.43	54.64	3.00	7.34	17.00
9	80	325	$C_{17}H_{10}N_2O_4S_2$	55.12	2.72	7.56	17.31
			370.41	5540	2.51	7.39	17.20
10	75	250	$C_{19}H_{14}O_3S_2$	64.38	3.98		18.09
			354.45	64.50	3.71		18.22
11	72	223	$C_{20}H_{16}O_3S_2$	65.19	4.38		17.40
			368.48	65.00	4.21		17.60
12	75	290	$C_{14}H_{10}N_2O_2S_2$	55.61	3.33	9.27	21.21
			302.38	55.40	3.30	9.00	21.00
13	65	150	$C_{20}H_{14}N_2O_2S_2$	63.47	3.73	7.40	16.94
			378.48	63.65	3.90	7.60	16.75
14	70	280	$C_{15}H_{11}N_3O_2S_2$	54.69	3.37	12.76	19.47
			329.41	54.49	3.15	12.50	19.60
15	62	212	$C_{15}H_{11}N_2O_2S_3$	51.85	3.19	8.06	27.69
			347.47	51.61	3.10	8.20	27.49
16	63	126	$C_{20}H_{13}NO_2S_3$	60.74	3.31	3.54	24.32
			395.46	60.94	3.46	3.31	24.52
17	62	173	$C_{16}H_{11}NO_2S_3$	55.63	3.21	4.05	27,84
			345.47	55.46	3.00	4.21	27.65

In anology with malononitrile and ethylcyanoacetate the reaction of compound **1** with a variety of active methylene compounds under the same experimental conditions (in aquas ethanol containing piperidine equivalent) gave the desired spiro heterocyclic compounds. Moreover reaction of compound **1** with pentane-2,4-dione afforded 3'-acetyl-2',6'-dimethylspiro[naphtho[2,3-*d*][1,3]dithiole-2,4'-pyran]-4,9-dione **6** and with ethylacetoacetate gave 3'-acetyl-2'-hydroxy-6'-methylspiro[naphtha[2,3-*d*][1,3]-dithiole-2,4'-pyran]-4,9-dione **7**.

The reaction of cyanoacetamide with compound **1** gave 2'-amino-6'-methyl-4,9-dioxo-4,9-dihydrospiro[naphtho[2,3-*d*][1,3]dithiole-2,4'-pyran]-3'-carboxamide **8**, while a clear evolution of NH_3 gas was observed during the reaction of cyanoaceto hydrazide with compound **1** with subsequent formation of fused pyrazolone ring namely, 6'-methyl-1',2'-dihydro-3'*H*-spiro[naphtho[2,3-*d*]-[1,3]dithiole-2,4'-pyrano[2,3-*c*]pyrazol]-3',4,9-trione **9**.

The reaction of compound **1** with cyclopentanone or cyclohexanone gave 2'-methyl-6',7'-dihydro-5'*H*-spiro-[naphtha[2,3-*d*][1,3]dithiolecyclopenta[*b*]-2,4'-pyran]-4,9-dione **10** and 2'-methyl-5',6',7',8'-tetrahydrospiro[naphtha-[2,3-*d*][1,3]dithiole-2,4'-chromene]-4,9-dione **11**, respectively (*c.f.* Scheme 2).

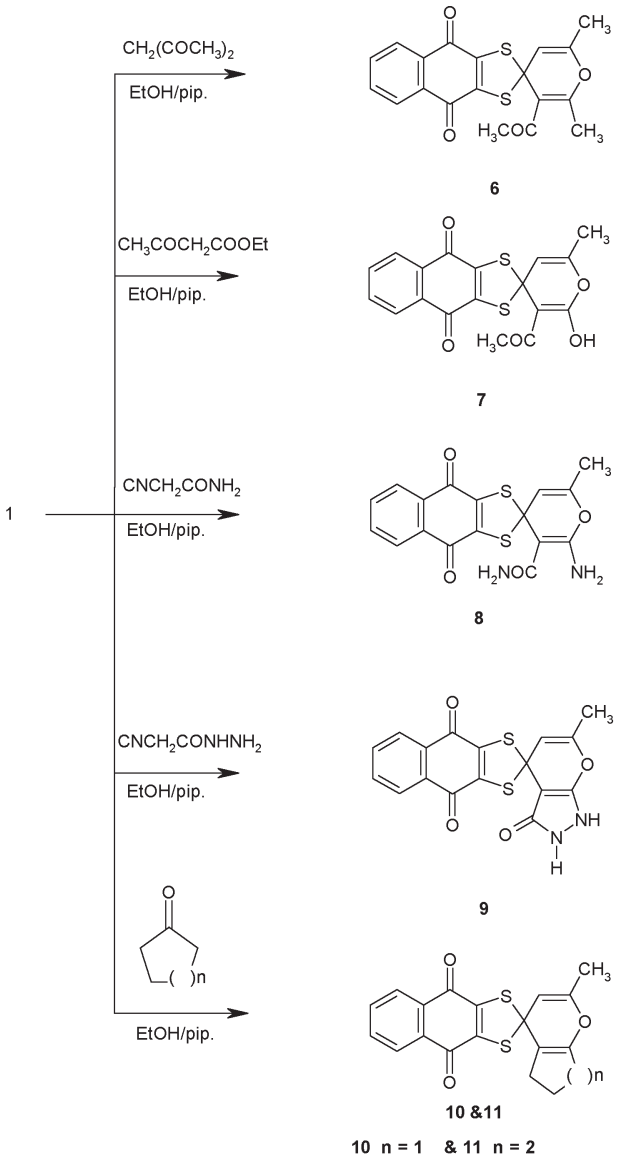
Compound **1** was allowed to react with another variety of bidentate compounds including hydrazine hydrate, phenylhydrazine and guanidine hydrochloride by using the same previous exeperimental reaction conditions to give the corresponding spiro heterocyclic compounds, 5'-methyl-2',4'-dihydrospiro[naphtho[2,3-*d*][1,3]dithiole-2,3'-pyrazole]-4,9-dione **12**, 5'-methyl-1'-phenyl-1',2'-dihydrospiro-[naphtha[2,3-*d*][1,3] dithiole-2,3'-pyrazole]-4,9-dione **13** and 2'-amino-6'-methyl-5'*H*-spiro[naphtha[2,3-*d*][1,3]dithiole-2,4'-pyrimidine]-4,9-dione **14**, respectively.

Also compound **1** was allowed to react with active hydrogen carrying reagents such as thiourea, *o*-aminothiophenol and thioacetamide where the corresponding spiro heterocyclic compounds were obtained namely, 2'-amino-4'-methylspiro[naphtho[2,3-*d*][1,3]dithiole-2,6'-[1,3]thiazine]-4,9-dione **15**, 4'-methyl-3*H*-spiro[naphtho[2,3-*d*]1,3]dithiole-2,2'-[1,5]-benzothiazepine]-4,9-dione **16** and 2',4'-dimethylspiro[naphtho[2,3-*d*][1,3]dithiole-2,6'-[1,3]thiazine]-4,9-dione **17**, respectively (*c.f.* Scheme 3).

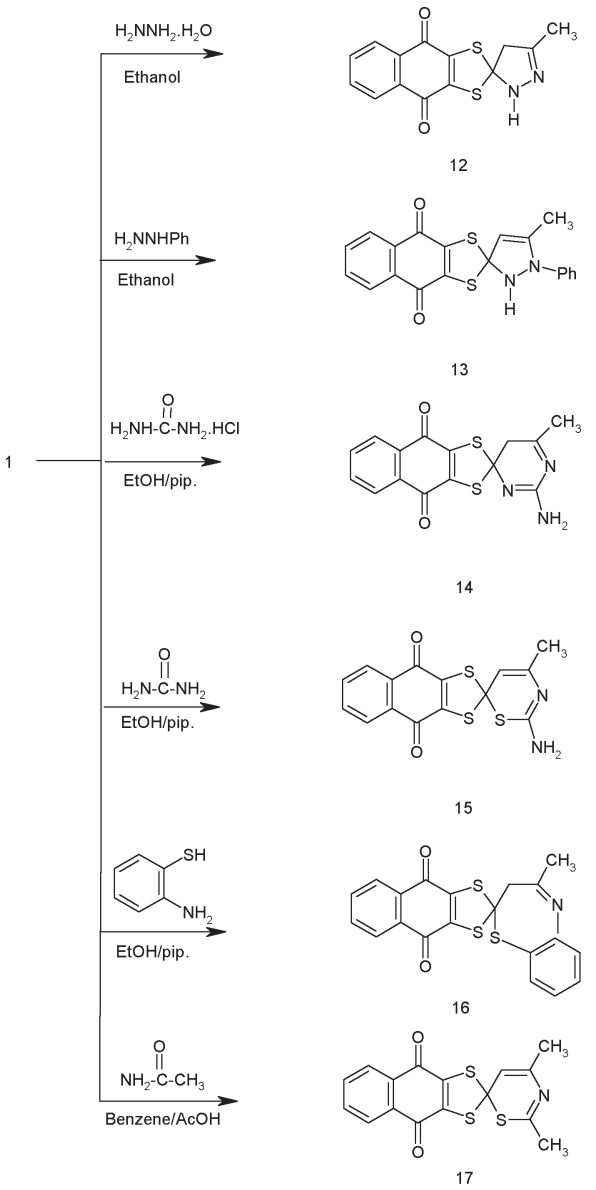
EXPERIMENTAL

All m.p. are uncorrected, IR spectra were obtained (KBr discs) on a Nicolate 710 FT-IR spectrometer. ^{1}H-NMR spectra were obtained on a Varian EM 360A at 60 MHz using an internal standerd. The elemental analyses were carried out on an elemental analyzer model 240c.

Scheme 2



Scheme 3



2(1-Acetyl-2-oxopropylidene)naphtho[2,3-*d*][1,3]dithiole-4,9-dione (**1**).

An equimolar mixture (5.26 mL, 50 mmol) of 2,4-pentandione and carbondisulphide (3.00 mL, 50 mmol) in 70 mL benzene was treated with 7 g of anhydrous K_2CO_3.The formed dianionic compound was then treated with (11.35 g, 50 mmol) of 2,3-dichloronaphthoquinone and a catalytic amount of tetrabutylammonium bromide (TBAB, 3 mmol). The reaction mixture was stirred for about 4 h at 60 °C and the benzene layer was separated by filtration, washed with water, dried over anhydrous sodium sulphate and evaporated *in vacuo*. The obtained solid was washed with light pet. Ether (40-60), collected by filtration and recrystallized from ethanol.

2(2-Oxopropylidene)naphtho[2,3-*d*][1,3]dithiole-4,9-dione (**2**).

Method A.

A mixture of compound **1** (3.30 g, 10 mmol) and sodium ethoxide (1 g of sodium in 30 mL of ethanol) was refluxed for 2 h. The precipitated solid was collected by filtration, washed with water and recrystallized from ethanol.

Method B.

A mixture of compound **1** (3.30 g, 10 mmol) and piperidine (1 mL) in 30 mL of ethanol was refluxed for 2 h. The precipitated solid was collected by filtration and recrystallized from ethanol.

Spiro Naphtho[2,3-*d*][1,3]dithiole-4,9-dione Derivatives **3-17**.

General Procedure.

Compound 1 (3.30 g, 10 mmol) and piperidine (1 mL) in 10 mL of aqueous ethanol was added to a stirred suspension of the appropriate reagent (10 mmol) in 15 mL aqueous ethanol. Then the reaction was refluxed over different periods of time, the

Table 2

IR and NMR Spectra of the Prepared Compounds

Comp. No.	IR (KBr) cm^{-1}	H^1-NMR(DMSO) ppm
1	3026 (CH-arom.), 2926(CH-aliph.), 1672(CO) naphthoquinone 1558, 1558 (CO)acetyl	8.70-8.30 (m, 4H, CHarom.), 2.30(s, 6H, $2CH_3$).
2	3025 (CH-arom.), 2930 (CH-aliph.), 1670 (CO naphtho.)1558, 1620(CO) acetyl	8.60-8.20 (m, 4H, CH, arom.), 5.20(s, 1H =CH), 2.30(s, 3H, CH_3).
3	3462, 3362 (NH_2), 2199 (CN), 1650 (CO)	8.30-7.90 (m, 4H, CH, arom.), 6.80-6.50 (br, 2H, NH_2), 6,00 (s, 1H, =CH), 2.30 (s, 3H, CH_3).
4	3470-3370 (NH_2), 2920 (CH,aliph), 1750 (CO ester), 1670 (CO)	8.20-7.90 (m, 4H, CH, arom.), 6.50 (s, 1H, =CH), 5.10 (br, 2H, NH_2), 4.20-3.90 (q, 2H, CH_2), 2.30 (s, 3H, CH_3), 1.30-1.00 (t, 3H, CH_3).
5	3450 (OH), 1990 (CN), 1670 (CO).	8.90 (s, 1H, OH), 8.10-7.80 (m, 4H, CH, arom.), 6.30 (s, 1H, =CH), 2.30 (s, 3H, CH_3).
6	1670 (CO), 1635 (CO, acetyl).	8.30-7.70 (m, 4H, CH, arom.), 5.90 (s, 1H, =CH), 2.40 (s, 3H, CH_3, acetyl), 2.20 (s, 3H, CH_3), 2.15 (s, 3H, CH_3).
7	3510 (OH), 1675 (CO), 1640 (CO, acetyl).	9.50 (s, 1H, OH), 8.40-8.10 (m, 4H, CH –arom.), 6.10 (s, 1H, =CH), 2.30 (s, 3H, CH_3), 2.20 (s, 3H, CH_3).
8	3350, 3275, 3150 (NH_2, $CONH_2$), 1670 (C=O naphth.), 1640 (C=O carboximide)	8.20-7.90 (m, 4H, CHarom.), 6.50 (s, 1H, =CH), 6.00-5.80 (br, 2H, NH_2), 5.40-5.20 (br, 2H, $CONH_2$), 2.30 (s, 3H, CH_3).
9	3458, 3354 (2NH), 1668 (C=O), 1640 (C=O pyrazol).	8.70 (s, 2H, 2NH), 8.30-8.00 (m, 4H, CH, arom), 6.30 (s, 1H, =CH), 2.30 (s, 3H, CH_3)
10	1665 (C=O).	8.30-8.00 (m, 4H, CH arom), 6.50 (s, 1H, =CH), 2.30 (s, 3H, CH_3), 1.80-1.30 (m, 6H, cyclic CH_2).
11	1668 (C=O)	8.30-8.00 (m, 4H, CH arom.), 6.40 (s, 1H, =CH), 2.30 (s, 3H, CH_3), 1.80-1.20 (m, 8H, cyclic CH_2).
12	3330 (NH), 3028 (CH arom.), 2930 (CH, aliph), 1670 (C=O)	10.00-9.60 (br, 1H, NH), 8.20-7.80 (m, 4H, CHarom), 2.20 (s, 3H, CH3), 1.60 (s, 3H, CH_3).
13	3350 (NH), 3028 (CH arom.), 2930 (CH aliph.), 1665 (C=O).	9.95-9.60 (br. 1H, NH), 7.90-6.90 (m, 9H, CHarom.), 5.80 (s, 1H, =CH), 2.30 (s, 3H, CH_3).
14	3335, 3250 (NH_2), 3030 (CH arom), 2955 (CH aliph.), 1667 (C=O).	8.10-6.60 (m, 4H, CH arom.), 5.50-5.20 (br, 2H, NH_2), 2.25 (s, 3H, CH_3), 1.65 (s, 2H, CH_2).
15	3365, 3278 (NH_2), 3030 (CH arom), 2927 (CH aliph.), 1665 (C=O).	8.10-7.50 (m, 4H, CH arom.), 6.50 (s, 1H, =CH), 5.30 (s, 2H, NH_2), 2.30 (s, 3H, CH_3).
16	3030 (CH arom.), 2942 (CH aliph.), 1668 (C=O).	8.10-7.00 (m, 8H, CH arom.), 2.25 (s, 3H, CH_3), 1.65 (s, 2H, CH_2).
17	3027 (CH arom.), 2935 (CH aliph.), 1663 (C=O).	8.15-7.80 (m, 4H, CHarom.), 6.70 (s, 1H, =CH), 2.30 (s, 6H, $2CH_3$).

resulting solid was collected by filteration and recrystallized from the proper solvent.

2'-Amino--6'-methyl-4,9-dioxo-4,9-dihydrospiro[naphtho[2,3-*d*]-[1,3]dithiole-2,4' pyran]-3'-carbonitrile (**3**).

Then the reaction mixture was refluxed for **1** hour. The solid that formed was collected by filtration and recrystallized from dimethylformamide into reddish brown crystals to yield **3**.

2'-Amino-6'-methyl-4,9-dioxo-4,9-dihydrospiro[naphtho[2,3-*d*]-[1,3]dithiole-2,4'-pyran]-3'-carboxylate **4** and 2'-Hydroxy-6'-methyl-4,9-dioxo-4,9-dihydrospiro[naphtho[2,3-*d*][1,3]dithiole-2-4'-pyran]-3'-carbonitrile **5**.

The reaction mixture was refluxed for 2 hours. The solid that formed was collected by filtration and recrystallized from ethanol into white crystals to yield compound **4**. The filtrate was concentrated, left to cool and the formed solid was collected by filtration and recrystallized from methanol into white crystals to yield **5**.

3'-Acetyl-2',6'-dimethylspiro[naphtho[2,3-*d*][1,3]dithiole-2,4'-pyran]-4,9-dione (**6**).

The reaction mixture was refluxed for 2 hours. The solid formed was collected by filtration and recrystallized from dioxan into yellow crystals to yield **6**.

3'-Acetyl-2'-hydroxy-6'-methylspiro[naphtho[2,3-*d*][1,3]dithiole-2,4'-pyran]-4,9-dione (**7**).

The reaction mixture was refluxed for 4 hours. After cooling the solid that formed was collected by filtration and recrystallized from ethanol into brown crystals to yield **7**.

2'-Amino-6'-methyl-4,9-dioxo-4,9-dihydrospiro[naphtho[2,3-*d*]-[1,3]dithiole-2,4'-pyran]-3'-carboxamide (**8**).

The reaction mixture was refluxed for 4 hours. After cooling the solid that formed was collected by filtration and recrystallized from ethanol into colourless crystals to yield **8**.

6'-Methyl-1',2'-dihydro-3'*H*-spiro[naphtho[2,3-*d*][1,3]dithiole-2,4'-pyrano[2,3-*c*]pyrazol]- 3',4,9-trione (**9**).

The reaction mixture was refluxed for 2 hours. The solid that formed was collected by filtration hot and recrystallized from dimethylformamide into yellow crystals to yield **9**.

2'-Methyl-6',7'-dihydro-5'*H*spiro[naphtho[2,3-*d*][1,3]dithiole-cyclopenta[*b*]-2,4'-pyran] -4,9-dione (**10**).

The reaction mixture was refluxed for 4 hours. After concentration and cooling the solid that formed was collected by filtration and recrystallized from ethanol into yellow crystals to yield **10**.

2'-Methyl-5',6',7',8'-tetrahydrospiro[naphtho[2,3-*d*][1,3]dithiole-2,4'-chromene]-4,9-dione (**11**).

The reaction mixture was refluxed for 4 hours. After concentration and cooling the solid that formed was collected by filtraton and recrystallized from ethanol into white crystals to yield **11**.

5'-Methyl-2',4'-dihydrospiro[naphtho[2,3-*d*][1,3]dithiole-2,3'-pyrazole]-4,9-dione (**12**).

The reaction mixture was stirred for an additional one hour. After concentration and cooling the solid that formed was collected by filtration and recrystallized from ethanol into red crystals to yield **12**.

5'-Methyl-1'-phenyl-1',2'-dihydrospiro[naphtha[2,3-*d*][1,3]dithiole-2,3'-pyrazole]-4,9-dione (**13**).

The reaction mixture was refluxed for 2 hours. After concentration and cooling the solid that formed was collected by filtration and recrystallized from ethanol into yellow crystals to yield **13**.

2'-Amino-6'-methyl-5'*H*-spiro[naphtha[2,3-*d*][1,3]dithiole-2,4'-pyrimidine]-4,9-dione (**14**).

The reaction mixture was refluxed for 2 hours. After concentration and cooling the solid that formed was collected by filtration and recrystallized from dimethylformamide into yellow crystals to yield **14**.

2'-Amino-4'-methylspiro[naphtho[2,3-*d*][1,3]dithiole-2,6'-[1,3]-thiazine]-4,9-dione (**15**).

The reaction mixture was refluxed for 2 hours. After concentration and cooling the solid that formed was collected by filtration and recrystallized from ethanol into yellow crystals to yield **15**.

4'-Methyl-3*H*-spiro[naphtho[2,3-*d*]1,3]dithiole-2,2'-[1,5]-benzothiazepine]-4,9-dione (**16**).

The reaction mixture was refluxed for 2 hours. After concentration and cooling the solid that formed was collected by filtration and recrystallized from ethanol into yellow crystals to yield **16**.

2',4'-Dimethylspiro[naphtho[2,3-*d*][1,3]dithiole-2,6'-[1,3]thiazine]-4,9-dione (**17**).

The reaction mixture was refluxed for 2 hours. After concentration and cooling the solid that formed was collected by filtration and recrystallized from ethanol into yellow crystals to yield **17**.

REFERENCES AND NOTES

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[1] R. H. Thompson, naturally Occuring Quinones, 2nd ed, Academic: New York, 1971.

[2] P. R. Rich, *Faraday Discuss. Chem. Soc*. **74**, 3183 (1982).

[3] B. L. Ed. Trumpower, Function of Quinones in Energy Conserving Systems, Academic: New York, 1982.

[4] R. A. Ed. Morton, Biochemistry of Quinines, Academic: New York 1965.

[5] R. H. Blum, S. K. Carter, *Ann. Int. Med*., **80**, 249 (1974).

[6] A. Di Marco, In Cancer Medicine, Holland, J, F, E. ,Eds., Frei, Lea & Febiger: Philadelphia, 872 (1982).

[7] T. Janaky, A.,Juhasz, S. Bajusz, V. Csernus, G. Srkalovic, L. Bokser, S. Milovanivic, T. W. Redding, Z. Rekasi, A. Nagy, V. Schally, *Proc. Acad. Sci. USA* **89**, 972 (1992).

[8] A. Thuillier and J. Vialle, *Bull. Soc. Chem.*, 1398 (1959).

[9] G. Kobayashi, Y. Matsuda and R. Natsuki, *Chem. Pharm. Bull.*, **21**, 921 (1973).

[10] S. Rajappa, R. Sreenivasan, B. G. Advani, R. H. Summerville and R. Hoffmann, *Indian J. Chem. Sect. B*, **15**, 297 (1977).

[11] M. Augustin and W. Doelling, *J. Prakt. Chem.*, **324**, 3 (1982).

[12] M. D. Nair and J. A. Desai, *Indian J. Chem. Sect. B*, **21**, 4 (1982).

[13] M. D. Nair, S. Rajappa and J. A. Desai, *Indian J. Chem. Sect., B* **21**, 1 (1982).

[14] S. Rajappa, M. D. Nair, R. Sreenivasan, and B. G. Advani, *Tetrahedron* **36**, 1673 (1982).

[15] Z. T. Huang, and Z. R. Liu, *Synthesis,* 357 (1987).

[16] K. Hirai, Y. Matsuda and H. Kishda, *Chem. Pharm. Bull.*, **20**, 97 (1971).

[17] S. Rajappa and B. G. Advani, *Proc. Indian Acad. Sci. (Chem. Sci.),* **91**, 463 (1982).

[18] Z. T. Huang and X. Shi, *Synthesis,* 162 (1990).

[19] A. K. El-Shafei, H. A. Abdel-Ghany, A. A. Sultan and A. M. M. El-Saghier, *Phosphorous Sulfur and Silicon*, **73**, 15 (1992).

[20] A. K. El-Shafei, A. M. M. El-Saghier, A. A. Sultan, and A. M. Soliman, *Phosphorous Sulfur and Silicon*, **72**, 73 (1992).

[21] A. A. Sultan, A. M. Soliman and A. K. El-Shafei, *Phosphorous Sulfur and Silicon*, **97**, 1 (1994).

[22] A. M. El-Sayed, A. M. M. El-Saghier, A. M. Ali and A. K. El-Shafei, *Gazzetta Chimica Italiana*, **127**, 605 (1997).