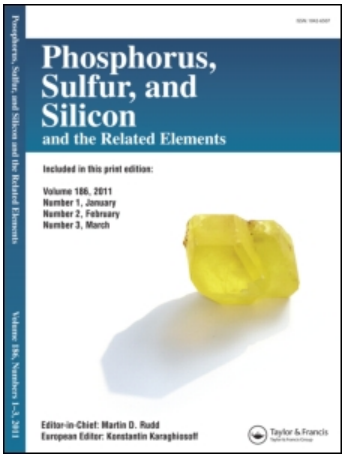

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HETEROCYCLES. A SIMPLE ONE-STEP SYNTHESIS OF SUBSTITUTED ENDO-NAPHTHOPHENOTHIAZINES

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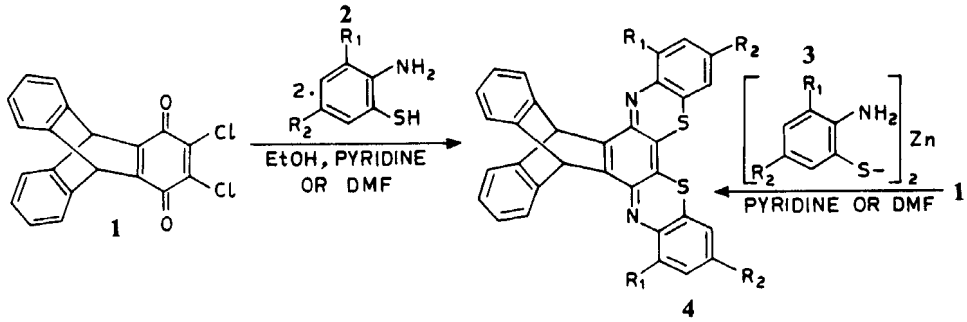
A number of substituted endo-12,17-*O*-phenylene-12,17-dihydronaphtho[2,3-a][1,4]benzothiazino[3,2'-c]phenothiazines (**4**) and substituted endo-8,13-*O*-phenylene-8,13-dihydro-6-chloro-7H-naphtho[2,3-a]phenothiazin-7-ones (**5**) were synthesised by the condensation reaction of endo-9,10-*O*-phenylene-2,3-dichloro-9,10-dihydro-1,4-anthraquinone (**1**) with substituted 2-aminothiophenol (**2**) and their zinc mercaptides (**3**), respectively. These reactions are rationalized and pertinent IR and UV data are also given.

In continuation of our interest in heterocyclic chemistry[2-11] we have synthesised a number of nuclear substituted benzophenoxazines, benzophenoxazones, 12H-benzo[b]phenoxazine-6,11-diones, benzophenazines, phenothiazines, benzophenothiazines, benzo[a][1,4]benzothiazino[3,2-c]-phenothiazines, and 12H-quinoxalo[2,3-b]phenoxazines. Phenothiazines have a number of uses in medicines such as tranquilisers,[12] anticancer drugs,[13] antiinflammatory agents,[14] antihistaminics,[15] anthelmintics,[16] local anaesthetics,[17] antiseptics[18] and in the treatment of neuropsychiatric disorders[19] and in industry as antioxidants,[20] stabilisers[21] and dyes.[22] Little attention has been paid to the synthesis of 14H-naphtho[2,3-b]phenothiazines which are excellent disperse dyes[23,24] and produce violet to green shades on polyester, polyamides and cellulose acetate fibres. The recorded syntheses of 14H-naphtho[2,3-b]phenothiazines[23,24] are tedious, lengthy, lead to low yield and are limited to a few nuclear-substituted derivatives. This stimulated our interest to develop a new method of synthesis of analogous nuclear substituted endo-naphtho[2,3-a]phenothiazines and also to examine their colouring and pharmaceutical properties.

The present communication records the first convenient, high yield, one-pot synthesis of a novel new class of nuclear substituted heterocycles, i.e. endo-8,13-*O*-phenylene-8-13-dihydro-6-chloro-7H-naphtho[2,3-a]phenothiazin-7-ones (**5**) and endo-12,17-*O*-phenylene-12,17-dihydronaphtho[2,3-a][1,4]benzothiazino[3',2'-c] phenothiazines (**4**). The infrared and ultraviolet data are presented.

For the synthesis of endo-naphtho[2,3-a]phenothiazines the use of Mine's reaction[25] was planned. It involves the reaction of substituted *p*-benzoquinone with zinc mercaptide of 2-aminothiophenol or free thiophenol in ethanol. The endo-9,10-*O*-phenylene-2,3-dichloro-9,10-dihydro-1,4-anthraquinone (**1**) was prepared and treated with substituted zinc mercaptides of 2-aminothiophenols under various reaction conditions. Condensation of **1** with substituted 2-aminothiophenol (**2**) in ethanol, pyridine or dimethylformamide gave **4** (Scheme 1). The **4** can also be obtained by the reaction of endo-9,10-*O*-phenylene-9,10-dihydro-1,4-dioxo-3-pyridinium-2-anthroxide (**6**) with substituted **2** in pyridine (Scheme 2).

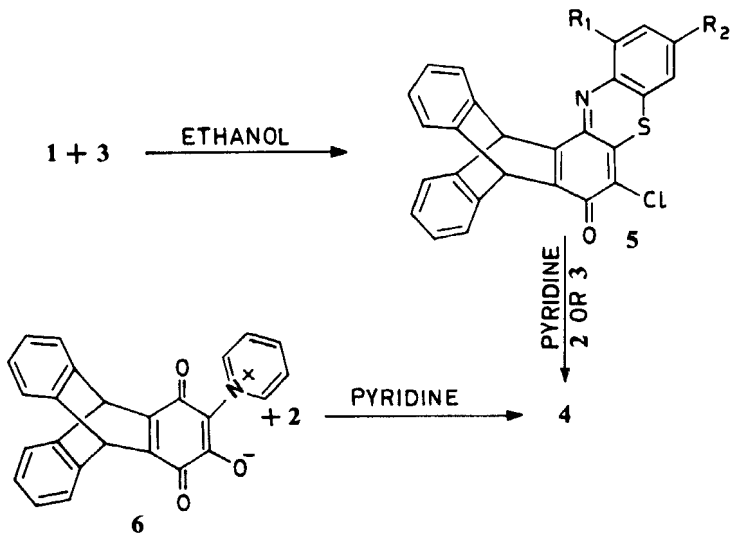


SCHEME 1

It is quite interesting to note that when **1** was condensed with the zinc salt of substituted 2-aminothiophenol (**3**) in ethanol, compound **5** was formed. However, it is of further interest to observe that the same reaction in dry pyridine or dimethylformamide gave **4**. Compound **4** can also be obtained by the reaction of **5** with **3** or **2** in pyridine or dimethylformamide. The best yield of **4** was obtained when the reaction of **1** was carried out with **2** in pyridine. All compounds produced characteristic colors with concentrated sulfuric acid.

It appears that compound **2** displays additional driving forces which enhance the reaction to form **4**. This argument is further strengthened by the fact that even **2** reacts with **6** to give **4**. The reaction appears to occur via Michael addition, mercaptide ion adding twice to the quinone system, with the elimination of hydrogen chloride and subsequent ring closure through the amino group.

In the latter reaction, **3** adds once to the quinone system with the elimination of water and zinc chloride and seems to be formed via Mine's reaction.[25] It seems that



SCHEME 2

TABLE I

Substituted endo-8,13-*O*-phenylene-8,13-dihydro-6-chloro-7H-naphtho[2,3-a]phenothiazin-7-ones(**5**)

R_1	R_2	M.P. (°C)	Yield (%)	Molecular formula	Analyses (calcd. %) C	H	N	Ir spectral data (C=O) cm^{-1} [a]	UV spectra data (λ_{max} Nm)[b]	Rf value for the system[c]
H	H	198	80	$C_{26}H_{14}ClNOS$	73.60 (73.67)	3.60 (3.30)	3.58 (3.31)	1670s	248,292	0.63
H	F	172	85	$C_{26}H_{13}FClNOS$	71.90 (71.56)	2.58 (2.97)	3.28 (3.20)	1650s	249,290 (Sh)	0.65
H	Cl	251	81	$C_{26}H_{13}Cl_2NOS$	68.05 (68.12)	2.59 (2.83)	2.85 (3.05)	1650s	252,290 (Sh)	0.67
H	Br	145.6 (dec)	78	$C_{26}H_{13}BrClNOS$	62.42 (62.09)	2.80 (2.58)	2.56 (2.78)	1645s	—	0.66
H	CH_3	239	87	$C_{27}H_{16}ClNOS$	74.40 (74.06)	3.50 (3.65)	3.42 (3.20)	1650s	251,297	0.64
H	OCH_3	264	68	$C_{27}H_{16}ClNO_2S$	71.85 (71.40)	3.60 (3.52)	3.20 (3.08)	1630s	—	0.52
H	OC_2H_5	267	72	$C_{28}H_{28}ClNO_2S$	71.90 (71.87)	3.56 (3.85)	2.85 (2.99)	1630s	—	0.58
Br	CH_3	225	65	$C_{27}H_{15}BrClNOS$	62.32 (62.54)	2.89 (2.89)	2.78 (2.70)	1660s	252,293 (Sh)	0.63

[a] Sharp.
[b] Shoulder.
[c] Toluene–hexane–acetone : : 70 : 20 : 10 (v/v).

TABLE II

Substituted endo-12,17-*O*-phenylene-12,17-dihydronaphtho[2,3-a][1,4]benzothiazino[3′,2′-c]phenothiazines(**4**)

R_1	R_2	M.P. (°C)	Yield % A	B	C	Molecular formula	Analyses (calcd. %) C	H	N	UV spectral data (λ_{max} Nm)[a]	Rf value for the solvent system[b]
H	H	211 (dec)	90	78	60	$C_{32}H_{18}N_2S_2$	64.88 (64.64)	3.23 (3.03)	4.79 (4.71)	215,250, 266 (Sh)	0.66
H	F	> 360	92	75	48	$C_{32}H_{16}F_2N_2S_2$	72.75 (72.45)	3.32 (3.01)	5.50 (5.28)	220,253	0.69
H	Cl	> 360	87	68	49	$C_{32}H_{16}Cl_2N_2S_2$	68.54 (68.20)	2.56 (2.84)	4.58 (4.58)	216,252	0.65
H	Br	205 (dec)	87	55	34	$C_{32}H_{16}Br_2N_2S_2$	58.98 (58.89)	2.60 (2.45)	3.95 (4.29)	215,252	0.64
H	CH_3	159	94	65	49	$C_{34}H_{22}N_2S_2$	78.58 (78.16)	3.81 (4.21)	5.62 (5.36)	221,252, 291 (Sh)	0.62
H	OCH_3	> 360	80	58	34	$C_{34}H_{22}N_2O_2S_2$	73.50 (73.64)	3.84 (3.97)	5.04 (5.05)	216,253, 310 (Sh)	0.53
H	OC_2H_5	235	78	59	37	$C_{36}H_{26}N_2O_2S_2$	74.85 (74.74)	4.50 (4.49)	4.95 (4.94)	218,252, 280 (Sh)	0.55
Br	CH_3	> 360	75	48	34	$C_{34}H_{20}Br_2N_2S_2$	59.85 (60.00)	2.80 (2.94)	2.58 (2.35)	236,252, 309 (Sh)	0.25

[a] Shoulder.
[b] Toluene–hexane–acetone : : 70 : 20 : 10.

zinc chloride generated during the reaction may inhibit further condensation by complexation with the product, but the presence of basic solvents may neutralise effects caused by zinc chloride. Additional evidence for this fact is supported because **5** and **2** in pyridine also gave **4**. The colouring and pharmaceutical properties will be reported elsewhere.

EXPERIMENTAL

All melting points are uncorrected. The purity of all compounds was checked by thin layer chromatography[26] on silica gel in various nonaqueous solvent systems. The substituted 2-aminothiophenols and their zinc mercaptides were synthesised by the method reported earlier.[5,11] Endo-9,10-*O*-phenylene-2,3-dichloro-9,10-dihydro-1,4-anthraquinone (**1**)[26] and endo-9,10-*O*-phenylene-9,10-dihydro-1,4-dioxo-3-pyridinium-2-anthroxide (**6**)[28] were prepared as reported in literature.

Synthesis of substituted endo-8,13-O-phenylene-8,13-dihydro-6-chloro-7H-naphtho [2,3-a]-phenothiazin-7-ones (**5**). A mixture of endo-9,10-*O*-phenylene-2,3-dichloro-9,10-dihydro-1,4-anthraquinone (**1**) (0.005 mol) and zinc mercaptide (**3**) (0.0025 mol) in 10 ml of ethanol was stirred for 1 hour at room temperature and then refluxed for 80 minutes. The solution was cooled, filtered, washed well with water and 10% hydrochloric acid, again with water and finally with dilute ethanol using suitable crystallising solvents; analytical samples were obtained (Table I).

Synthesis of substituted endo-12,17-O-phenylene-12,17-dihydronaphtho[2,3-a][1,4]benzothiazino[3',2'-c]phenothiazines (**4**)

Method (A). A mixture of **1** (0.005 mol) and substituted 2-aminothiophenol (0.01 mol) in 5–7 ml dry pyridine was stirred for 30 minutes and then refluxed under gentle heating for 3 hours. An equal volume of methanol was added and the reaction mixture was chilled, filtered and worked as above (Table II).

Method (B). A mixture of **1** (0.005 mol) and substituted zinc mercaptide of 2-aminothiophenol (0.005 mol) in 10 ml pyridine was stirred for 1 hour and then refluxed for 3 hours. The process remains as above. The desired product was isolated by column chromatography on alumina using toluene as eluant.

Method (C). A mixture of substituted endo-8,13-*O*-phenylene-8,13-dihydro-6-chloro-7H-naphtho[2,3-a]phenothiazin-7-one (**5**) (0.0025 mol) and substituted 2-aminothiophenol (0.0025 mol) in 10 ml pyridine was refluxed gently for 3 hours and worked up as in Method A.

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