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Derivatives of 14H-Naphtho[2,3-a]phenothiazine-8,13-dione—III. Syntheses via Boric Acid Complexes of α-Hydroxy-anthraquinones

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ABSTRACT

The reaction of α-hydroxy (and amino) derivatives of anthraquinone with 2-aminobenzenethiol in the presence of boric acid is evaluated. The formation of the resulting 14H-naphtho[2,3-a]phenothiazine-8,13-diones proceeds with greater facility than with previously reported reactions in the absence of boric acid, giving products in generally good yield and high purity. The use of ethanolic media, such as 2-methoxyethanol, is more convenient than alternative methods involving, for example phenol or Zn/HCl in the reaction system. Copyright © 1996 Elsevier Science Ltd

INTRODUCTION

The condensation reaction between 2-aminobenzenethiol and 1,4-dihydroxy-(amino) anthraquinones substituted in either the hydroxylated[1] or unsubstituted ring[2] has been previously reported. The principal reaction medium used in these investigations was DMF at elevated temperature, although *N*-methylpyrrolidone and DMSO were equally effective. With some of the intermediates used, lower temperatures and/or the use of ethanolic solvents was necessary in order to obviate side reactions.[2]

We report here some preliminary studies on the formation of **I** and related derivatives by interaction of various α-hydroxy(amino)anthraquinones with

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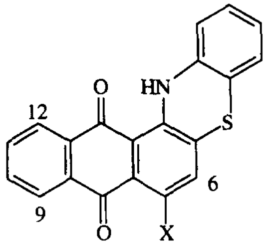
2-aminobenzenethiol in the presence of boric acid, and a comparison of the facility of the reaction relative to previously reported procedures.



I.1 X = H ; **I.2** X = OH

I.3 $X = NH_2$; **I.4** X = NHPh

I.5 $X = NHC_6H_4CH_3$ - 4[1]

EXPERIMENTAL

General

The anthraquinone starting materials used were sourced as previously noted.[1,2] Electronic spectra were recorded on a Philips PU 8730 spectrophotometer and mass spectra on an AEI MS 902. Column chromatography was carried out on Silica Gel (for column chromatography, Acros), applying the colourants from solution in chlorobenzene and eluting with toluene containing 0–15% ethyl acetate as appropriate.

Reactions in phenol

The appropriate anthraquinone derivative (0.002 mol) and boric acid (0.62 g, 0.01 mol) were stirred into molten phenol (20 g) at 110–120°C for 30 min. 2-Aminothiophenol (2.5 g, 0.02 mol) was added and the mixture stirred at 135–140°C until all starting material had reacted. The liquor was cooled to 70–80°C, ethanol (20 ml) added and the mixture stirred slowly into 10% aq. KOH (80 ml) and stirring continued for 1 h. After filtering, the presscake was washed with 5% KOH, then with water, and finally with methanol.

The resulting products were purified by column chromatography. Yields shown are for pure material thus isolated. Compounds **I.1**–**I.3** were identical to those previously described.[3]

From 1-hydroxyanthraquinone, 2 h reaction time, 82% of **I.1**.

From 1,4-dihydroxyanthraquinone, 1 h, 80% of **I.2**.

From 1-amino-4-hydroxyanthraquinone, 90 min, 75% of a mixture of **I.2** and **I.3** in an approximate ratio of 2:1.

From 1,5-dihydroxyanthraquinone, 2 h, 72% of 9-hydroxy-14H-naphtho-[2,3-a]phenothiazine-8,13-dione (**II**), dark blue needles, m.p. 251–252°C. *M/z* (EI) 345, M^+, 100%. λ_{max}, nm (log e) in chlorobenzene: 624 (3.98).

From 1,8-dihydroxyanthraquinone, 3 h, 67% of 12-hydroxy-14H-naphtho-[2,3-a]phenothiazine-8,13-dione (**III**), blue–black needles, m.p. 267–268°C. *M/z* (El) 345, M^+, 100%. λ_{max}, nm (log e) in chlorobenzene: 615 (4.11).

Reactions in Zn/HCl

The appropriate anthraquinone derivative (0.002 mol) and boric acid (0.62 g, 0.01 mol) were stirred into conc. HCl at 75–80°C and Zn dust (0.05 g) was added. After stirring for 30 min, 2-aminothiophenol (2.5 g, 0.02 mol) was

TABLE 1

Condensations of Anthraquinone (AQ) Precursor (0.002 mole) with 2-Aminobenzenethiol (0.02 mole) and Boric Acid (0.02 mole) in 2-Methoxyethanol. Formation of Mono-condensed Derivatives

AQ intermediate	Reaction time	Yield	Product	Reaction time in DMF (Ref. 1)
1-OH	45 min	87%	I.1	18 h
1,4-(OH)$_2$	30 min	85%	I.2	3 h
Leuco-1,4-(OH)$_2$	20 min	90%	I.2	—
1,4-(OH)$_2$-2-OPh	10 min	85%	I.2	45 min
1,4-(OH)$_2$-2-SPh	10 min	90%	I.2	30 min
1,4-(OH)$_2$-2-NH$_2$	90 min	75%	I.2	20 h
1,2,4-(OH)$_3$	30 min	85%	I.2	3 h
1,4-(NH$_2$)$_2$	90 min	80%	I.3	72 h no reaction
Leuco-1,4-(NH$_2$)$_2$	45 min	80%	I.3	—
1-OH-4-(NH$_2$)$_2$	40 min	85%	I.2/I.3 (a)	20 h (I.2)
1-OH-2-Br-4-NH$_2$	20 min	85%	I.3 (b)	5 h (I.2)
1-OH-3-Br-4-NH$_2$	20 min	80%	I.2 (b)	20 h (I.2)
1-OH-4-NHPh	40 min	85%	I.4/I.2 (c)	4 h (I.2)
1-OH-2-Br-4-NHPh	20 min	80%	I.4	3 h
1-NH$_2$-4-NHPh	60 min	85%	I.3/I.4 (d)	72 h no reaction
1-NH$_2$-2-Br-4-NHPh	30 min	85%	I.4 (e)	3 h
1-NH$_2$-2-Br-4-NHC$_6$H$_4$.Me-4′	30 min	85%	I.5 (e)	3 h
1,4-(NHPh)$_2$	2 h	80%	I.4	48 h no reaction
1,5-(OH)$_2$	2 h	75%	II	—
1,8-(OH)$_2$	2.5 h	68%	III	—

(a) Two products, separated by chromatography (I.3:I.2 3:2).
(b) *Ca.* 5% of I.2/I.3, respectively, also formed; removed on recrystallisation (charcoal).
(c) Two products, separated by chromatography (I.2:I.4 1:2.5).
(d) Two products, separated by chromatography (I.3:I.4 2:3).
(e) *Ca.* 5–10% of I.3, removed on recrystallisation (charcoal).

added and stirring continued at 85–90°C until all starting material had reacted. The viscous liquor was cooled, diluted with methanol (25 ml), stirred for 30 min and filtered. The residue was washed with cold methanol and purified by column chromatography.

From 1-hydroxyanthraquinone, 90 min, 72% of **I.1**.
From 1,4-dihydroxyanthraquinone, 1 h, 81% of **I.2**.
From 1,5-dihydroxyanthraquinone, 90 min, 62% of **II**.

Reactions in 2-methoxyethanol.

The anthraquinone derivative (0.002 mol) was stirred for 30 min under reflux in 2-methoxyethanol (20 ml) with addition of boric acid (0.62 g, 0.01 mol). 2-Aminothiophenol (2.5 g, 0.01 mol) was added and refluxing continued until all starting material had reacted. The liquor was cooled, diluted with methanol (20 ml) and stirred for 5–30 min prior to filtering. The (usually) crystalline residue was washed with warm water and finally with warm methanol to remove residual thiol. Pertinent reaction times for mono-condensation and product data are shown in Table 1.

Using a similar procedure, but with increased amounts of boric acid (0.02 mol) and 2-aminobenzenethiol (up to 0.08 mol, as noted in Section 3), bis-condensed derivatives were obtained, viz:

11,12-Dithia-6H, 17H, 6,17-diazadinaphtho[3,2-a][2,3-c]-5,18-anthraquinone (**IV**), m.p. >350°C (lit.[4] 246–247°C). *M/z* (EI) 450, M^+, 100%. λ_{max}, nm (log e) in chlorobenzene: 589 sh (3.69), 652 (3.90) and 712 (3.89).

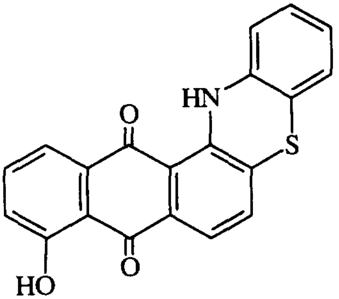
3,12-Dithia-8H, 17H, 8,17-diazadinaphtho[3,2-c][3,2-f]-9,18-anthraquinone (**V**), m.p. >350°C. $C_{26}H_{14}N_2O_2S$ requires: C, 69.3; H, 3.1; N, 6.2; S, 14.2. Found: C, 69.0; H, 2.8; N, 5.9; S, 14.0%. *M/z* (EI) 450, M^+, 100%. λ_{max}, nm (log e) in chlorobenzene: 660 (4.21).

3,10-Dithia-9H, 18H, 9,18-diazadinaphtho [3,2-c][2,3-d]-9,18-anthraquinone (**VI**), m.p. >350°C. Found: C, 68.8; H, 2.9; N, 6.0; S, 13.8%). *M/z* (EI) 450, M^+, 100%. λ_{max}, nm (log e) in chlorobenzene: 684 (4.19).

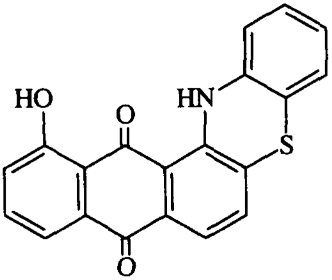
RESULTS AND DISCUSSION

The use of boric acid as reaction additive during the synthesis of anthraquine dyes and intermediates is well established. Typically, the formation of a complex between boric acid and 1,4-dihydroxyanthraquinone greatly facilitates interaction with arylamines to give 1,4-bis-arylamino derivatives. Similar reactions with 1,8-dihydroxy-5-nitro-4-arylaminoanthraquinone results in the formation of 1-aminated derivatives,[5,6] compared to the more conventional nucleophilic replacement of the 5-nitro group which occurs in the absence of boric acid. Formation of a boric acid complex also influences electrophilic substitution. Thus, alizarin undergoes nitration at the 4-position in the absence of boric acid but at the 3-position in the presence of boric acid, due to loss of the mesomeric influence of the 1-hydroxy group. Similarly, formation of a boric acid complex with 1,4-dihydroxy-anthraquinone inhibits chlorination in the 2,3-positions, the product being the 5,8-dichloro derivative.

Some preliminary investigations were therefore made on the reaction between some α-hydroxyanthraquinones with 2-aminobenzenethiol in the presence of boric acid using previously reported reaction media, viz phenol[5,6] and Zn/HCl.[7,8] The results (see Experimental) showed that formation of the phenothiazine derivatives occurred more readily than in previously reported reactions in DMF.[1] Thus, 1-hydroxyanthraquinone gave **I.1** in 1.5–2 h, compared to 18h in DMF; 1,4-dihydroxyanthraquinone similarly showed a decreased reaction time (1 h cf. 3 h). The reaction of 1,5- and 1,8-dihydroxyanthraquinone with 2-aminobenzenethiol has not been previously reported; evaluations in DMF at 135–140°C in the present study showed neither compound to have undergone any significant reaction after 72 h. Both isomers, however, underwent relatively facile conversion to the monocondensed derivatives **II** and **III** over 2–3 h in the phenolic medium, but whilst anthrarufin gave similar reaction in Zn/HCl, little formation of **III** was apparent from chrysazin over 8 h reaction.



II



III

Both methods, however, have disadvantages. Work-up of the product from the phenolic medium was tedious, total elimination of residual phenol being necessary to ensure a readily filterable end-liquor, and the products required chromatographic separation to attain pure material. The Zn/HCl reactions tended to produce very viscous reaction media, difficult to stir and maintain accurate temperature control. Chromatography was necessary in product purification, in contrast to the relatively pure products obtained directly from DMF reaction liquors,[1,2] albeit over a longer reaction period.

Reactions in 2-methoxyethanol were found to be equally effective and considerably more user-friendly. For comparison with the previously reported data for reactions in DMF,[1] the reaction conditions were arbitrarily standardised using a 10 mol excess of 2-aminobenzenethiol. The data in Table 1 clearly indicates the enhanced facility for formation of the mono-condensed derivatives **I.1–I.5** in the presence of boric acid. Thus, 1-hydroxy-anthraquinone gave good conversion to **I.1** in 45 min, whereas in DMF a reaction time of 18 h was necessary. 1,4-Dihydroxyanthraquinone afforded **I.2** in 30 min (3 h in DMF) and a similarly shortened reaction time is apparent for all the anthraquinone intermediates used. Compared to the phenolic and Zn/HCl systems, reaction products were usually recovered in good yield as high-purity crystalline material after dilution of the reaction liquor with methanol, filtering and washing with warm methanol. Chromatographic separations were necessary only in cases where the reaction product contained two components of type **I** (see Table 1).

Reactions with 1-amino-2-bromo-4-hydroxyanthraquinone and 1-amino-3-bromo-4-hydroxyanthraquinone were more specific than those in DMF, in which debromination and formation of **I.2** occurred in both cases over a relatively prolonged reaction time.[1] In 2-methoxyethanol/boric acid, reaction was complete in 20–30 min, giving essentially **I.2** and **I.3**; small amounts of **I.3/I.2** were eliminated after product recrystallisation. Both products resulted from the reaction with 1-amino-4-hydroxyanthraquinone indicating that, under the reaction conditions used, α-aminoanthraquinones were also reactive in absence of a labile β-substituent. This was additionally evident in the rapid formation of **I.3** from 1,4-diaminoanthraquinone; when using DMF alone, no reaction was evident after 72 h.[1]

Further differences were apparent in reactions with 1-hydroxy-4-arylamino- and 1-amino-4-arylaminoanthraquinones. Whereas in DMF, 1-hydroxy-4-arylaminoanthraquinones reacted with elimination of the arylamino moiety and formation of **I.2**, and 1-amino-4-arylaminoanthraquinones were unreactive,[1] in the 2-methoxyethanol/boric acid medium, competitive reactions occurred, with formation of mixtures of **I.2** and **I.4/I.5**. More selective product formation occurred when the corresponding 2-bromo derivatives were used as precursors, with good conversion to **I.4/I.5** occurring. The latter compounds were also obtained from 1,4-bis-arylaminoanthraquinones, although over a more extended reaction time (2 h); no reaction occurred with these compounds in DMF after 60 h.

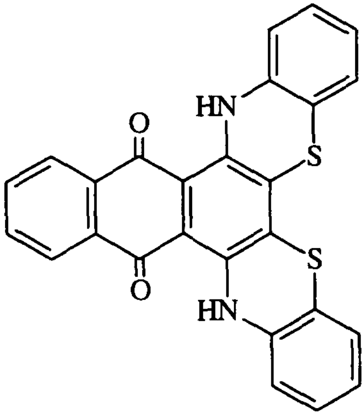
In many of the reactions shown in the Table 1 indication of the formation of bis-condensed products was also apparent. Thus, after the initial formation of **I.2** from 1,4-dihydroxyanthraquinone was completed within 30 min, continued reaction resulted in the gradual formation of the bis-condensed derivative **IV**. After 10 h, work-up and chromatography afforded **I.2** and

IV in an approximate 3:2 ratio; similar results pertained with 1-amino-4-hydroxy-, 1,2,4-trihydroxy-, 1-hydroxy-4-anilino- and 1,4-diaminoanthraquinones. The formation of the bis-condensed derivatives was enhanced by increasing the mol ratios of boric acid and, especially, 2-aminobenzenethiol. Typically, 0.002 mol anthraquinone derivative, 0.02 mol boric acid and 0.05 mol 2-aminobenzenethiol showed conversion to **IV** over 8–12 h, although various by-products were evident (TLC), some, but not all, of which were removed on methanol washing. Under these conditions, both 1,5- and 1,8-dihydroxyanthraquinones required 10–20 h for formation of bis-condensed material. Contamination with other reaction products occurred to a significant extent, and whilst orange and red coloured components were eliminated on methanol washing, a major violet component was not. This had a similar R_f value to the required bis-condensed material, and its formation appeared to be related to some form of self-condensation of 2-aminobenzenethiol. Simulated reactions in absence of any anthraquinone based precursor showed gradual formation of a deep violet liquor over a 20–30 h period; it was concluded that elimination of the violet contaminant required less stringent reaction conditions.

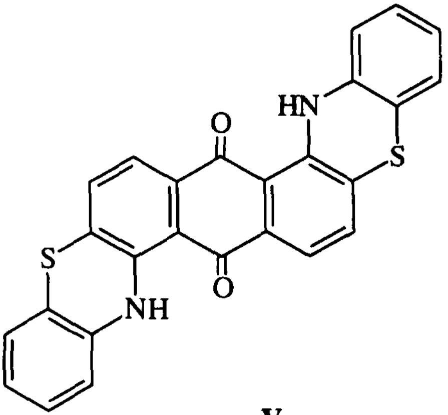
Bis-condensation reactions were therefore carried out using the basic reactants as described earlier, but with progressive increase in the amount of thiol used. For most reactions, it was found that 0.08 mol thiol gave satisfactory results over a relatively shorter reaction time. Under these conditions, 80–90% of **IV** was obtained, after standard methanol dilution, filtering and methanol washing, from 1,4-dihydroxyanthraquinone (4–5 h), leuco-1,4-dihydroxyanthraquinone (3–4 h), 1-amino-4-hydroxyanthraquinone (4–5 h), 1,4-diaminoanthraquinone (5–6 h) and 1-hydroxy-4-arylaminoanthraquinones (5–6 h).

More prolonged reaction times were necessary for the bis-condensation reaction for 1,5- and 1,8-dihydroxyanthraquinones, and even with 0.08 mol of thiol the times required were such as to result in formation of the violet–blue contaminant. Reactions were therefore carried out for 10 h and 24 h, respectively, which afforded **V** and **VI** in 44 and 42%, respectively, following exhaustive methanol wash of the initially precipitated material and subsequent repeated recrystallisations (charcoal) from 2-methoxyethanol. These results indicate the considerably decreased facility for bis-condensation from these isomers relative to 1,4-dihydroxyanthraquinone.

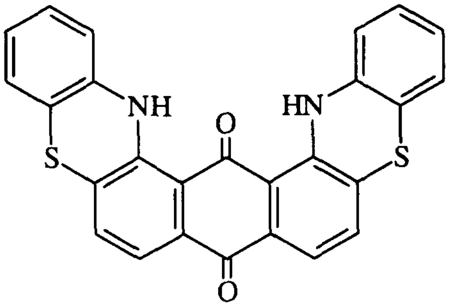
Electronic spectra parameters for various mono- and bis-condensed derivatives are given in Table 2. It is evident that conjoint substitution in the same phenyl ring of the anthraquinone moiety by the hetero system and a hydroxy group is the most advantageous for colour development. Comparisons between the 6- and 7-hydroxy (**I.2**) derivatives have been previously discussed,[2] and introduction of the hydroxy group into the unsubstituted



IV



V



VI

phenyl ring, viz 9-(**II**) and 12-hydroxy derivatives (**III**) results in much more limited colour shifts. The absorption spectra of **II** and **III** show only one major resolved band, equating approximately to the lower wavelength resolved absorption band of **IV**.

The bis-condensed derivatives from 1,5- and 1,8-dihydroxyanthraquinone (**V** and **VI**) show the anticipated bathochromic shifts relative to **II** and **III** respectively, but not to an extent comparable to those observed with **IV**. In general, their λ_{max} values can be approximated to that of the mono-condensed

TABLE 2

Electronic Spectra Data, λ_{max} (log e) in Chlorobenzene for Mono-hydroxy Derivatives of 14H-Naphthol[2,3-a]phenothiazine-8,13-dione, and of Bis-condensed Derivatives

Substituent		λ_{max} (log e)				
—		584	(3.88)			(Ref. 1)
6-OH		560 sh	(3.34)	603 (407)	641 (401)	(Ref. 1)
7-OH	(I.2)	584 sh	(3.69)	625 (415)	682 (407)	(Ref. 1)
9-OH	(II)	624	(3.98)			
12-OH	(III)	615	(4.11)			
	IV	589 sh	(3.69)	652 (3.90)	712 (3.89)	
	V	660	(4.21)			
	VI	684	(4.19)			

derivative **I.2**. As in anthraquinone dyes generally, therefore, the largest bathochromic shifts are obtained with a '1,4-' substitution pattern, and for the bis-substituted derivatives reported in this investigation no advantages are gained colourwise from a '1,5-' or '1,8-' substitution. This does not, however, preclude the use of such orientations in attaining potential NIR absorption in more heavily substituted compounds.

CONCLUSIONS

The use of 2-methoxyethanol/boric acid as reaction medium in the condensation of α-hydroxy- and aminoanthraquinones with 2-aminobenzenthiol offers a relatively user-friendly and facile method for the generation of derivatives of 14H-naphtho[2,3-a]phenothiazine-8,13-dione. Reaction times are short and products can be isolated in good yield and purity. Whilst not specifically noted in this report, ethanol can also be used as solvent, but reaction times tend to be increased (up to 50% for facile reactions); however, with less reactive precursors such as chrysazin and anthrarufin this solvent is not satisfactory.

The method gives ready access to mono- and bis-condensed products without the requirement of a labile substituent[1,2] in the β-position, and hence offers the potential for the synthesis of a wide range of products from more readily accessible anthraquinone starting materials (the synthesis of β-substituted derivatives of which would entail tedious procedures). Further studies pertaining to this will be reported in the future.

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