Heteroannulation of Naphthoquinones. Studies on the Reaction of 2-Bromo-2,3-dihydronaphthoquinone Derivatives with 1,2-Binucleophiles.

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Dedicated to the memory of Professor Nicholas Alexandrou

Heterocyclic derivatives of naphthoquinones were synthesized *via* their 2-bromo-2,3-dehydro-intermediates. This new route may lead to the formation of benzo[*a*]phenothiazin-5-ones, benzo[*f*]quinoxalin-6-ones as well as their 1,4 (or 7,10) dihydroxy-derivatives in high yields. The possible mechanisms involved in the formation of these compounds are discussed.

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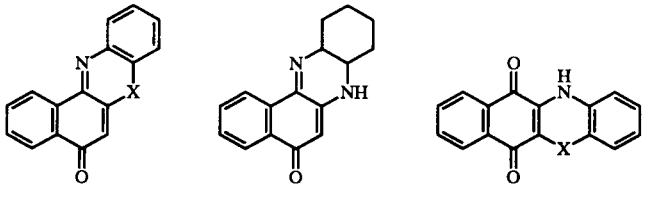
Introduction.

Heteroannulated naphthoquinones are receiving much attention due to their planar delocalized π-electronic structure and rich redox chemistry. For example, benzo[*a*]phenothiazin-5-ones, benzo[*a*]phenoxazin-5-ones, benzo[*a*]phenazin-5-ones and octahydrobenzo[*a*]-phenazin-6-ones of the general formulae **1**, **2**, **3** and **4** respectively (Scheme 1), have been reported to show interesting physicochemical properties [1]. In addition, these heterocyclic frameworks are components of molecules with significant biological activity or pharmacological properties, such as the neuroprotectant NRQX [2] and the antitumor agents BAP [3] and actinomycin D [4]. Recently, benzo[*b*]phenothiazine-6,11-diones and benzo-[*b*]phenoxazin-6,11-diones of the general formulae **5** and **6**, have been reported as unique compounds exhibiting semiconducting properties since they posses the "electron donor-*spacer*-electron acceptor (D-σ-A)" system, in the same molecule [5].

Scheme 1



1, X = S
2, X = O
3, X = NH

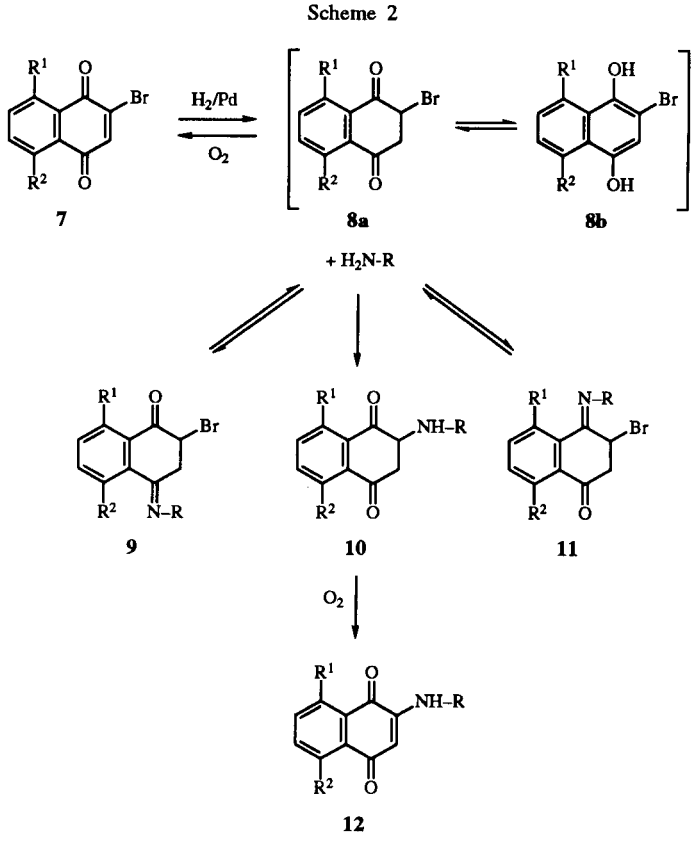
4

5, X = S
6, X = O

The common synthetic pathways for the preparation of the above compounds involve the condensation of quinones or 2,3-dichloroquinones with the respective amino-derivatives [6]. However, since these methods are tedious and tend to give rather low yields, there is a strong need for alternative synthetic routes [7].

In this article we present the results of ongoing research aiming at the development of a new methodology for the efficient preparation of heteroannulated naphthoquinones. This approach is an application of a recently reported method for the derivatization of naphthoquinones [8]. It is known that the reaction of halonaphthoquinones with nucleophiles gives a complex mixture of products [9].

Scheme 2

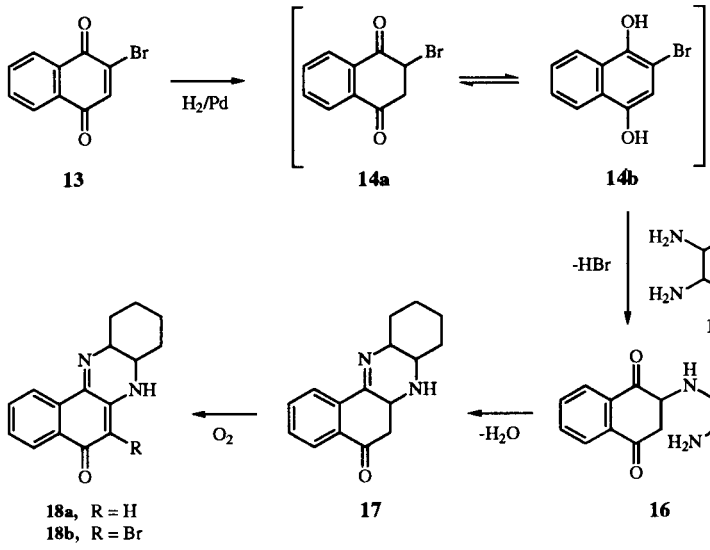


7 **8a** **8b**

9 **10** **11**

12

Scheme 3



13 14a 14b

Nevertheless, bromonaphthoquinones **7** under catalytic hydrogenation conditions are transformed to the leuco form **8** (Scheme 2), which readily reacts with nucleophiles, giving much cleaner reaction mixtures. For example, the addition of 2 equivalents of aliphatic amines to **8** (R^1 = R^2 = OH), followed by air oxidation, cleanly afforded the adduct **12** in almost quantitative yield [8], while the same reaction with bromoquinone **7** ($R^1 = R^2$ = OH) required 10 equivalents of the amine, resulting in the formation of adduct **12** in about 5% yield, together with all the other possible adducts, as well as polymeric material [10].

Results and Discussion.

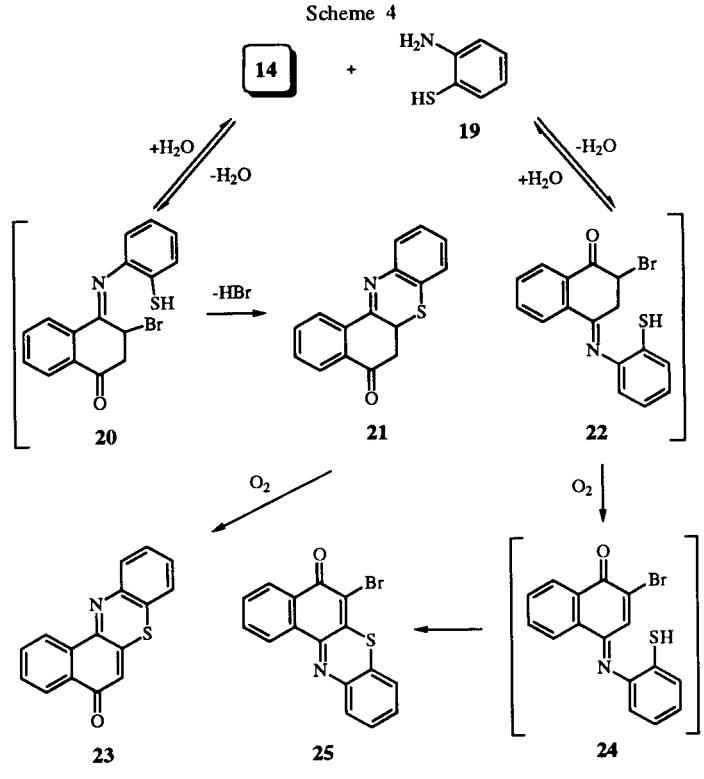
A. Reactions of Binucleophiles with 2,3-Dihydro-2-bromonaphthoquinone.

As an extension of the aforementioned methodology, we decided to investigate the reaction of 2,3-dihydro-2-bromonaphthoquinone with 1,2-binucleophiles. Treatment of a solution of 2-bromonaphthoquinone **13** (Scheme 3) with a catalytic amount of Pd/C under hydrogen, gave the dihydroquinone **14a**.

The predominant product of the reaction of **14a** with 1,2-diaminocyclohexane **15** in the presence of 4Å molecular sieves (5 minutes reaction time prior to air oxidation) is iminoquinone **18a** (71%). Only a small amount (19%) of the bromoquinone **18b** was observed (Table 1, entry 1). We suggest that, in this case, the main pathway [11] is a rapid displacement of bromine by nitrogen, followed by formation of Schiff base and concomitant ring closure (Scheme 3). This mechanism is in accordance with our previously reported results [8] for a series of simple aliphatic amines.

On the other hand, when 2-aminothiophenol **19** was used as the binucleophile, under the same reaction conditions, the product ratio was reversed (Scheme 4). Thus, we obtained bromoiminoquinone **25** as the major product (65% yield) and iminoquinone **23** as the minor one (15%, Table 1, entry 3). The ratio of products **25** vs. **23** was again reversed, when the same reaction was carried out in the absence of molecular sieves and over a longer reaction time (48% and 15% respectively, Table 1, entry 5). Apparently, this reaction proceeds *via* a different mechanism than the one shown in Scheme 3, due to the lower nucleophilicity of the aromatic amine and thiol group. In order to interpret these results, we proposed the mechanism shown in Scheme 4.

Scheme 4



The first step of this mechanism is the condensation of 2-aminothiophenol with **14a**, resulting in the formation of the two possible bromoimines **20** and **22**. In the absence of molecular sieves these can interconvert through the free hydroquinone **14a**. Formation of imine **20** is kinetically disfavored because of the presence of the bromine atom in the α-position. Under these conditions, however, only the bromo imine **20** can further react by an intramolecular nucleophilic substitution reaction. Thus, nucleophilic displacement of the bromine by sulfur yields the tetracyclic thiazine intermediate **21**, which is converted to iminoquinone **23** during the subsequent air-oxidation stage. In the case of bromo imine **22** we do not expect an intramolecular nucleophilic displacement reaction, since such a possibility would entail the formation of a seven membered ring. Upon oxidation of **22** however, the sulfur nucleophile adds to the newly formed enone moiety of **24** (intramolecular Michael addition) producing bromo imine **25**. In addition, we observed that the less nucleophilic *o*-aminoaniline does not react at room temperature with substrate **6a**.

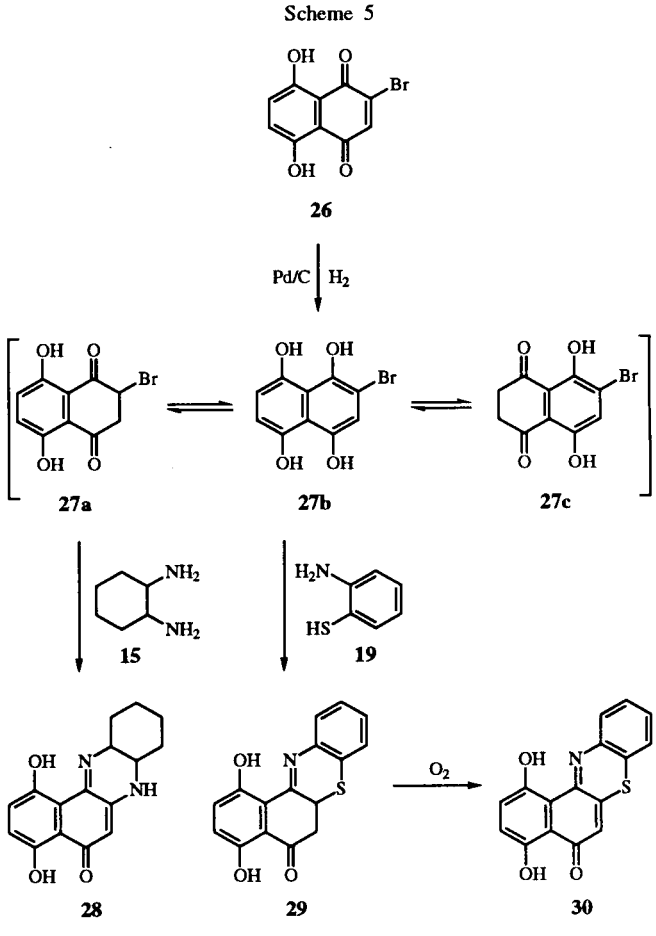
An alternative explanation for the observed formation of both imines **23** and **25** would entail rapid conversion of bromo imine **25** to imine **23**, by photolytic loss of bromine. In order to investigate such a possibility, we stirred a solution of the bromo imine **25**, under the given reaction conditions (ethyl acetate, air, ambient light) and followed the reaction by tlc, for several hours. We thus verified that the rate of conversion of **25** to **23** is extremely low, if not negligible, in non-polar solvents (ethyl acetate, benzene, dichloromethane). In order to observe a relatively fast conversion we had to resort to the use of a very polar solvent system (aqueous acetone). Therefore, we are further convinced that iminoquinone **23** isolated from our experiments is produced predominantly *via* the competitive imine formation mechanism shown in Scheme 4. This mechanism should also partially take place with binucleophile **15** (Scheme 3), explaining thus the formation of compound **18b**. Finally, when the experiment was repeated in the presence of 4Å molecular sieves, allowing the reaction to proceed for 24 hours prior to air oxidation, iminoquinone **25** was still the predominant product, although the ratio of products **25:23** (52:19%, Table 1, entry 4) was slightly changed in favor of the quinone **23**, presumably due to slow loss of bromine, as shown above.

In conclusion, we have observed that the ratio of iminoquinones III (*e.g.*, **18a** Scheme 3 or **23** Scheme 4) *vs.* the bromoiminoquinones IV produced (*e.g.*, **18b** Scheme 3 or **25** Scheme 4), depends on the nature of the binucleophile used and on the presence or absence of a water scavenger agent in the reaction mixture.

B. Reactions of Binucleophiles with 2-Bromo-5,8-dihydroxy-1,4-naphthoquinone.

The same reaction conditions were then applied to 2-bromo-5,8-dihydroxy-1,4-naphthoquinone **26**. As it is depicted in Scheme 5, **27** may exist in three tautomeric forms. Addition of diamine **15** in a solution of **27** and subsequent exposure of the reaction mixture to atmospheric oxygen, afforded compound **28** as the sole product (87% yield). Presumably isomer **27a** reacts exclusively with diamine **15** and the bromine moiety of the substrate is directing the addition. When binucleophile **19** was added in the reaction mixture of **27**, the outcome was again regiospecific and compound **30** was isolated in high yield (82%) after subsequent air oxidation of intermediate **29**. Surprisingly, in this particular case the leucoform **29** was relatively stable and could be isolated and characterized (see Experimental).

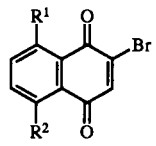
Scheme 5



Since no bromo-derivatives were isolated out of the above reactions, we conclude that addition to 2-bromoleuconaphthazarine **27** proceeds *via* a substitution mechanism (analogous to the one presented in Scheme 3) either with the strong nucleophile **15** or the weaker one **19**. Finally, treatment of **27** with the less nucleophilic *o*-aminoaniline, resulted only in fast debromination of the starting material.

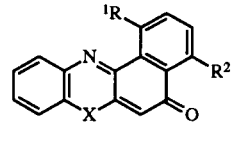
Table 1

Reagents and Conditions for the Formation of Heteroannulated Benzoquinones III and IV

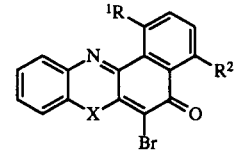


I

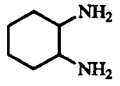
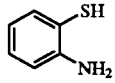
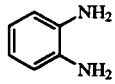
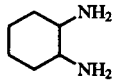
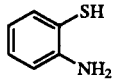
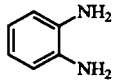
II



III



IV

Entry	Substrate I			Binucleophile II	Reaction Conditions			Products and yields				
	R^1	R^2			MS [a]	Equivalents of II	Time	Product	Yield	X	Product	Yield
1	H	H	13		+	1.2	5 minutes	**18a**	71%	NH	**18b**	19 %
2					–	1.2	24 hours	**18a**	52%	NH	**18b**	8 %
3	H	H	13		+	1.2	5 minutes	**23**	15%	S	**25**	65 %
4					+	1.2	24 hours	**23**	19%	S	**25**	15 %
5					–	1.2	24 hours	**23**	48%	S	**25**	15 %
6	H	H	13		+	3	45 minutes	no reaction				
7	OH	OH	26		–	2.4	15 minutes	**28**	87%	NH	–	
8	OH	OH	26		–	2.4	15 minutes	**30**	82%	NH	–	
9	OH	OH	26		–	2.1	15 minutes	debromination of **20**				

[a] Molecular sieves +(with), –(without).

Conclusion.

6-Bromo-5*H*-benzo[*a*]phenothiazin-5-one and 5-bromo-4*H*-benzo[*f*]quinoxalin-6-one (compounds **IV**, Table 1) are synthesized from the condensation of 2,3-dihydronaphthoquinone and the respective binucleophile. Des-bromo products (compounds **III**, Table 1) are formed predominantly when the same reactions are carried out in the absence of the dehydrating agent. Furthermore, the dihydroxylated derivatives of the above compounds may be synthesized in high yields using 2-bromoleuconaphthazarine as the starting material.

EXPERIMENTAL

General Methods.

All melting points, in degrees Centigrade, were determined in open capillary tubes with a Buchi melting point apparatus and are uncorrected. Reaction progress was followed with analytical thin-layer chromatography (tlc) performed on 0.25 mm silica gel precoated glass plates with fluorescent indicator UV_{254} (Merck). All column chromatography was done by the flash chromatography technique using 32-63 λm silica gel packing (Merck). The nmr spectra were recorded on a Bruker AC-200 spectrometer (operating at 200 MHz for proton and 50 MHz for carbon) in the solvents indicated. Chemical shifts are reported in parts per million downfield from tetramethylsilane (δ scale). The ir spectra were recorded on a Perkin Elmer Model 283 B (4,000-200 cm^{-1}) spectrophotometer from samples prepared in accordance with the potassium bromide disk technique. Peaks are reported in cm^{-1}. Mass spectra were obtained on a VG Trio 1000 spectrometer operating in electron impact mode at 70eV. Microanalytical data were provided by the NRC "Democritos", Athens, Greece. Reagents were purchased at analytical reagent grade. All solvents were used as received.

General Procedure.

A solution of bromonaphthoquinone in ethyl acetate containing 10% (by weight of bromonaphthoquinone) of Pd/C 10%, was stirred under hydrogen for 45 minutes. Then 4Å molecular sieves (1:1 by weight of bromonaphthoquinone) and a solution of the binucleophile in ethyl acetate were added and the reaction mixture was stirred under hydrogen for an additional period (see Table 1). The mixture was then acidified with acetic acid, stirred at open air for 10-20 minutes, filtrated through a small Celite pad and washed with 2*N* hydrochloric acid and water. The organic layer was dried over sodium sulfate and the solvents were removed under reduced pressure. The resulted residue was further purified by chromatography using hexane:ethyl acetate 80:20 as eluant or by crystallization.

5,7,7a,8,9,10,11,11a-Octahydrobenzo[*a*]phenazin-5-one (**18a**) and 6-Bromo-5,7,7a,8,9,10,11,11a-octahydrobenzo[*a*]phenazin-5-one (**18b**).

2-Bromonaphthoquinone **13** (50 mg, 0.21 mmole) in 7 ml of ethyl acetate was treated under hydrogen according to the general procedure using (+/-)-*trans*-1,2-diaminocyclohexane **15** (26.7 mg, 0.23 mmole) in 0.7 ml of ethyl acetate. Chromatographic separation afforded 37 mg (71%) of compound **18a** and 13 mg of compound **18b** (19%).

Compound **18a** was obtained as yellow crystals from ether, mp 126-128°; R_f = 0.1 (hexane:ethyl acetate 7:3); ir: ν_{max} 3250, 3100 br, 2925, 1685, 1175, 810, 620 cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.23 (m, 1H, H_4), 8.10 (m, 1H, H_1), 7.59-7.56 (m, 2H, H_2-H_3), 5.71 (s, 1H, H_6), 5.15 (br s, 1H, NH), 3.34 (m, 1H, $H_{11\alpha}$), 3.04 (m, 1H, $H_{7\alpha}$), 2.08-1.84 (m, 4H, CH_2), 1.42-1.39 (m, 4H, CH_2); ^{13}C nmr: CH, 131.5, 130.7, 125.5, 123.8, 101.9, 63.4, 53.3, CH_2, 32.1, 31.2, 25.5, 24.0; ms: m/z 252 (100), 209 (40), 196 (25), 128 (25), 77 (30), 69 (35), 43 (55).

Anal. Calcd. for $C_{16}H_{16}N_2O$ (252.13): C, 76.15; H, 6.40; N, 11.11. Found: C, 76.32; H, 6.34; N, 10.97.

Compound **18b** was obtained as yellow crystals from ether, mp 145-148°; R_f = 0.44 hexane-ethyl acetate 7/3); ir: ν_{max} 3470, 3365, 2920, 2850, 1605, 1555, 1260, 1090, 785 cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.17 (m, 2H, H_1-H_4), 7.59-7.48 (m, 2H, H_2-H_3), 5.46 (br s, 1H, NH), 3.32 (m, 1H, $H_{11\alpha}$), 3.18 (m, 1H, $H_{7\alpha}$), 2.13-1.92 (m, 4H, CH_2), 1.61-1.41 (m, 4H, CH_2); ms: m/z 332 (80), 330 (92), 289 (73), 287 (65), 250 (100), 127 (68), 77 (78).

Anal. Calcd. for $C_{16}H_{15}N_2OBr$ (330.04): C, 58.18; H, 4.58; N, 8.49. Found: C, 58.12; H, 4.64; N, 8.43.

5*H*-Benzo[*a*]phenothiazin-5-one (**23**) and 6-Bromo-5*H*-benzo[*a*]phenothiazin-5-one (**25**).

2-Bromonaphthoquinone **13** (50 mg, 0.21 mmole) in 7 ml of ethyl acetate was treated under hydrogen according to the general procedure using 2-aminothiophenol **19** (29.1 mg 0.23 mmole) in 0.7 ml of ethyl acetate. Chromatographic separation afforded 10.8 mg (15%) of compound **25** and 26.7 mg of compound **23** (48%).

Compound **23** was obtained as orange crystals from ether, mp 164-165°; R_f = 0.15 (hexane:ethyl acetate 9:1); ir: ν_{max} 2920, 1625, 1258, 1050, 795 cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.87 (d, 1H, J = 6.0, H_4), 8.30 (d, 1H, J = 6, H_1), 7.93 (d, 1H, J = 7.0, H_{11}), 7.75-7.73 (m, 2H, H_2-H_3), 7.47-7.42 (m, 3H, H_8-H_9-H_{10}), 6.84 (s, 1H, H_6); ^{13}C nmr: CH, 133.1, 131.9, 131.6, 130.2, 128.4, 126.8, 126.1, 125.0, 120.4; ms: m/z 263 (100), 235 (87), 203 (20), 190 (22), 117 (88), 68 (65).

Anal. Calcd. for $C_{16}H_9NSO$ (263.04): C, 72.99; H, 3.45; N, 5.32. Found: C, 73.17; H, 3.26; N, 5.21.

Compound **25** was obtained as red crystals from ether, mp 204-205°; R_f = 0.33 (hexane:ethyl acetate 9:1); ir: ν_{max} 2910, 1630, 1285, 1080 br, 750, 680 cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.95 (d, 1H, J = 7.8, H_4), 8.43 (d, 1H, H_1), 8.07 (d, 1H, J = 7.3, H_{11}), 7.84-7.77 (m, 2H, H_2-H_3), 7.65-7.58 (m, 3H, H_8-H_9-H_{10}); ^{13}C nmr CH, 133.1, 132.0, 131.6, 130.3, 128.4, 126.8, 126.1, 125.0; ms: m/z 342 (100), 340 (95), 314 (18), 234 (40), 190 (55), 116 (28).

Anal. Calcd. for $C_{16}H_8NSOBr$ (340.95): C, 56.31; H, 2.36; N, 4.11. Found: C, 56.29; H, 2.21; N, 4.05.

1,4-Dihydroxy-5,7,7a,8,9,10,11,11a-octahydrobenzo[*a*]phenazin-5-one (**28**).

2-Bromo-5,8-dihydroxy-1,4-naphthoquinone **26** (50 mg, 0.18 mmole) in 6 ml of ethyl acetate was treated under hydrogen according to the general procedure without molecular sieves, using (+/-)-*trans*-1,2-diaminocyclohexane **15** (46.8 mg, 0.41 mmole) in 0.7 ml ethyl acetate. After the usual work up the residue was crystallized from ethyl acetate-hexane to yield 46 mg (87%) of compound **28**.

Compound **28** was obtained as deep blue crystals from benzene, mp 226-227°; R_f = 0.44 (hexane:ethyl acetate 5:5); ir: ν_{max} 3410, 2920, 1635, 1540, 1340, 1100 br cm^{-1}; ^1H nmr (deuteriochloroform), δ 14.52 (s, 1H, OH hydrogen bonded), 12.04 (s, 1H, OH hydrogen bonded), 7.01-6.92 (m, 2H, H_2-H_3), 5.94 (s, 1H, H_6), 5.32 (br s, 1H, NH), 3.38-3.09 (m, 2H, $H_{7\alpha}$-$H_{11\alpha}$), 2.25-1.82 (m, 4H, CH_2), 1.59-1.12 (m, 4H, CH_2); ^{13}C nmr CH, 134.2, 132.2, 108.6, CH_2, 57.1, 64.3, 30.4, 30.3, 24.3, 23.8; ms: m/z 284 (38), 241 (18), 149 (15), 84 (92), 69 (95), 43 (100).

Anal. Calcd. for $C_{16}H_{16}N_2O_3$ (284.12): C, 67.58; H, 5.68; N, 9.86. Found: 67.74; H, 5.79; N, 9.73.

1,4-Dihydroxy-5*H*-benzo[*a*]phenothiazin-5-one (**30**).

2-Bromo-5,8-dihydroxy-1,4-naphthoquinone **26** (50 mg, 0.18 mmole) in 6 ml of ethyl acetate was treated under hydrogen according to the general procedure without molecular sieves, using 2-aminothiophenol **19** (50 mg, 0.41 mmole). After the usual work up the residue was crystallized from ethyl acetate-hexane to yield 45 mg (82%) of compound **30**.

Compound **30** was obtained as deep blue crystals from ethyl acetate-hexane, mp 240°; R_f = 0.43 (hexane:ethyl acetate 8:2); ir: ν_{max} 3450 br, 1615, 1575, 1445, 1235, 1215, 810, 745 cm^{-1}; ^1H nmr (deuteriochloroform): δ 14.64 (s, 1H, OH hydrogen bonded), 13.49 (s, 1H, OH hydrogen bonded), 7.57 (d, 1H, J = 7.3, H_2 or H_3), 7.35-7.18 (m, 5H, aromatic), 6.84 (s, 1H, H_6); ^{13}C nmr: CH, 134.6, 128.9, 128.4, 127.8, 127.4, 125.3, 121.1; ms: m/z 295 (100), 263 (18), 210 (24), 147 (15), 43 (47).

Anal. Calcd. for $C_{16}H_9NSO_3$ (295.03): C, 65.08; H, 3.07; N, 4.75. Found: C, 64.82; H, 3.25; N, 4.53.

1,4-Dihydroxy-6,6a-dihydro-5*H*-benzo[*a*]phenothiazin-5-one (**29**).

The reaction was carried out as for compound **30**. After completion of the reaction the mixture was concentrated under reduced pressure and chromatographed through a small column using ethyl acetate:hexane 1:9 as eluant. The product was partially decomposed, however the first fractions afforded compound **29** as yellow crystals.

Compound **29** was obtained as yellow crystals from ethyl acetate-hexane, mp 154-156°; R_f = 0.7 (benzene); ir ν_{max} 3400 br, 2900, 2810, 1620, 1585, 1440, 1050 br, 780 cm^{-1}; ^1H nmr (deuteriochloroform): δ 15.71 (s, 1H, OH hydrogen bonded), 11.97 (s, 1H, OH hydrogen bonded), 7.44-7.15 (m, 6H, aromatic), 4.13 (dd, 1H, J = 12.4, J = 7.0, H_{6a}), 3.30 (dd, 1H, J = 7.0, J = 16.8, H_{6ax}), 3.07 (dd, 1H, J = 12.4, J = 16.8, H_{6eq}); ms: m/z 297 (100), 268 (22), 252 (20), 186 (28), 84 (88), 43 (45).

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[11] The minor product is formed *via* a different pathway presented in Scheme 4 and discussed therein.