Preparation and Reactivity of Polyfunctional Phenazine Derivatives

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Treatment of 2,3,6,7-tetramethylphenazine with *N*-bromosuccinimide under light irradiation afforded in good yield the tetrakis(bromomethyl) derivative. Weakly basic nucleophilic reagents such as thiols, phenols, amines and the azide anion allow the preparation of a variety of functionalized derivatives. Some 2,7-disubstituted phenazines have also been obtained.

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Introduction.

The incorporation of planar heterocyclic dye molecules into macrocyclic structures may be expected to yield receptor molecules of cyclointercaland type that may bind selectively flat substrate molecules by stacking [1], interact with nucleic acids and their components [2] [3] and display electroactivity and photoactivity.

Phenazine and phenazinium derivatives [4] are of interest in this respect since they are planar and rigid, possess suitable electro and photochemical features and may present stacking interactions with planar substrates [5] in analogy to acridine dyes. They have been shown to undergo photoreduction [6], to mediate electron transfer [7] and to bind to nucleic acids [8].

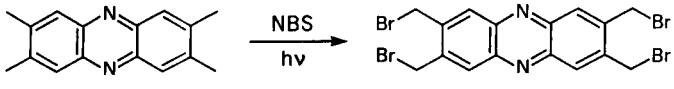
Along these lines, cyclointercalands containing two phenazine [9] and two acridine [10] groups have been synthesized recently.

In this context we have been led to investigate the preparation and reactivity of multifunctional phenazine derivatives of potential interest as reactive intercalating groups and as elements for incorporation into macropolycyclic structures.

We describe here the preparation of 2,3,6,7-tetrakis-(bromomethyl)phenazine **1** and its reactions with various nucleophiles that may lead to functionalized intercalating units.

I-Preparation of 2,3,6,7-Tetrakis(bromomethyl)phenazine 1.

2,3,6,7-Tetrakis(bromomethyl)phenazine **1** was obtained by bromination of 2,3,6,7-tetramethylphenazine **2** [11] with *N*-bromosuccinimide (NBS) in refluxing carbon tetrachloride.



2 **1**

When the reaction was performed in the presence of a free radicals initiator (benzoyl peroxide or azobisisobutyronitrile) it gave a complex mixture of polybrominated compounds. But by using an excess of NBS and by irradiating the mixture overnight with an ordinary 100 W tungsten light bulb the tetrabromo derivative **1** was obtained in 38% yield after one crystallization from toluene. It is worth noting that, even with an excess of NBS, the ^{1}H nmr spectrum of the crude product showed no formation of gem dibromo derivatives.

II-Reactivity of 2,3,6,7-Tetrakis(bromomethyl)phenazine 1.

In order to incorporate the phenazine group into macropolycyclic structures we first studied the reactions of various nucleophilic agents with the tetrabromo derivative **1**.

1-Oxygen Derivatives.

Dropwise addition of alcoholates, such as sodium methylate, to a solution of **1** in tetrahydrofuran immediately gave a dark precipitate insoluble in the common solvents. On the other hand, reaction with phenol in tetrahydrofuran at reflux in the presence of potassium carbonate yielded the tetraether **3** quantitatively (Scheme I). Carboxylate ions reacted very slowly even when added in large excess.

2-Nitrogen Derivatives.

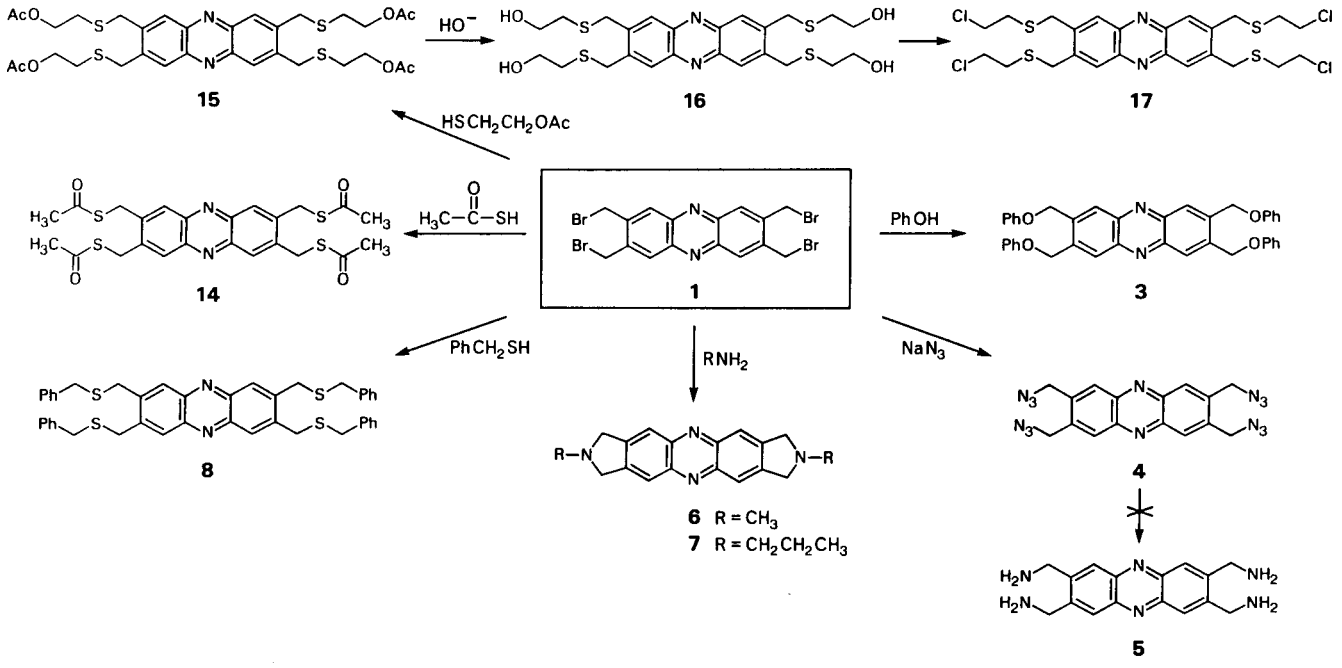
The reaction of sodium azide with **1** in acetonitrile gave the tetraazide **4** (76% yield) but the transformation of this azide into the corresponding tetraamine **5**, a very promising compound for the elaboration of macrocyclic structures, was not successful.

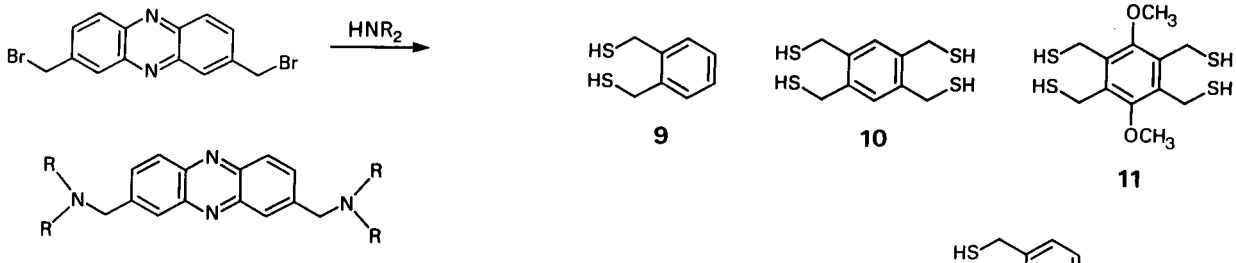
Catalytic reduction (hydrogen/Pd or hydrogen/platinum oxide) led to hydrogenolysis and tetramethylphenazine **2** was obtained. Chemical reductions with triphenylphosphine [12,13], triethylphosphite [12,14], sodium telluride [15] or stannous chloride (16) afforded unidentified insoluble products.

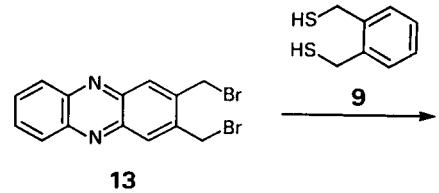
The reaction of secondary amines with 2,7-bis(bromomethyl)phenazine is known to give 2,7-bis(*N*,*N*-dialkylaminomethyl)phenazine derivatives [17].

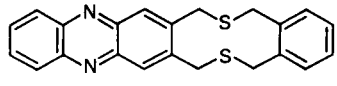
The yield depends on the nature of the amine; for instance, dioctylamine added in stoichiometric quantities gives the diaminophenazine in 53% yield. The same reac-

Scheme I









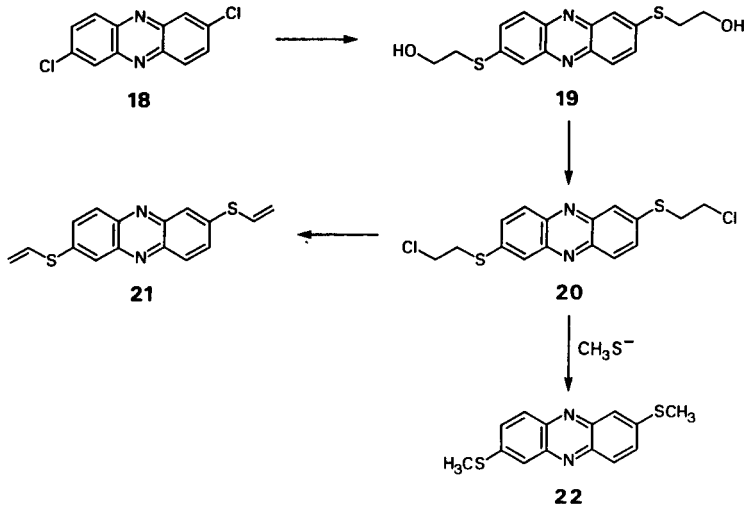
tion with 2,3,6,7-tetrakis(bromomethyl)phenazine afforded an insoluble dark powder, thus revealing the particular reactivity of the tetrasubstituted derivative. On the other hand, primary amines, in excess, gave pyrrole derivatives such as **6** and **7** (55-60% yield). Whatever the conditions tried, reactions with tosylamides afforded decomposition products with precipitation of insoluble dark powders.

3-Sulfur Derivatives.

Dropwise addition of benzylmercaptan to a solution of **1**, in tetrahydrofuran at reflux, in the presence of potassium carbonate, yielded the expected tetrasulfide **8**. However the condensation with di- and tetrathiols **9**, **10** and **11** gave rapid decomposition with precipitation of an insoluble dark solid; the only product remaining in the solution was the intermolecular disulfide. This reactivity is all the more unexpected as the derivative **12** was prepared (45% yield) by condensation of one equivalent of 2,3-bis(bromomethyl)phenazine **13**, synthesized in the same manner as **1**, with one equivalent of dithiol **9**.

Reaction of thiolacetic with **1**, in tetrahydrofuran, at reflux, in the presence of potassium carbonate gave the tetrathioester **14** (80% yield). The preparation of the corresponding tetrathiol was not successful. Both saponification or reduction of **14** gave an insoluble dark powder. Under the same conditions as with thiolacetic acid the reaction of ethyl 2-mercaptoacetate with **1** afforded **15** (61% yield) which after saponification gave tetraalcohol

Scheme II



16 (95% yield). This alcohol was converted into the corresponding chloride **17** by treatment with thionyl chloride (32% yield). This derivative showed an unexpected lack of reactivity. Halogen atoms situated in the β-position from a sulfur atom are known to be very reactive [18]. But in the case of **17** various oxygen, sulfur or nitrogen nucleophiles did not give the expected substitution products; the starting material was recovered. A similar abnormal reactivity was found again with the disubstituted phenazine derivative **20** synthesized in the following way (Scheme II). Reaction of 2,6-dichlorophenazine **18** [19,20] with 2-mercaptoethanol, in ethanol at reflux in the presence of sodium hydroxide gave **19** (*c.a.* 100% yield) which was converted to the dichloride derivative **20** (46% yield) by treatment with thionyl chloride. As with **17**, it was impossible to perform a nucleophilic substitution of the chloride atom. Too basic nucleophiles, such as alcoholate or tosylamide anions, gave only the α, β-unsaturated sulfide **21** (identified by its nmr spectrum) resulting from an elimination reaction. But a less basic nucleophile, such as the methylthiolate anion gave 2,6-bis(thiomethyl)phenazine **22** (identified by comparison with an authentic sample [21]).

Conclusion.

Although 2,3,6,7-tetrakis(bromomethyl)phenazine **1** is a most interesting building block for the synthesis of polyfunctional molecule of the intercalator type, its reactivity limits its use. The problems encountered could arise from the oxidative properties of the phenazine group combined with the fact that *para*-bisbromo methyl derivatives may give eliminations followed by polymerizations, thus making it difficult to control the reactions.

Only good, but not too basic, nucleophiles such as RS^-, ArO^- or N_3^- gave a nucleophilic substitution of the bromine atom, opening the way to tetrasubstituted phenazine derivatives. Further elaboration may still be envisaged (for instance reaction with cysteine). Since the phenazine group possesses a variety of features, these compounds may be endowed with interesting biological properties.

EXPERIMENTAL

All melting points were determined on a Kofler hot bench. The ^1H nmr spectra were recorded on a 200 MHz-Brucker instrument with tetramethylsilane as the internal standard; chemical shifts are in ppm. Absorption spectra were run on a Perkin-Elmer 554 spectrophotometer.

2,3,7,8-Tetrakis(bromomethyl)phenazine **1**.

A mixture of 5.22 g (22.1 mmoles) of tetramethylphenazine **2** [11] and 12.5 g (98.3 mmoles) of *N*-bromosuccinimide in 1200 ml of refluxing carbon tetrachloride was irradiated overnight with a 100 W tungsten light bulb. After filtration and evaporation of the solvent the crude material was dissolved in about 1 l of chloroform. This solution was washed with water, dried with sodium sulfate and evaporated. The resulting solid was washed with 100 ml of diethyl ether and crystallized from 290 ml of toluene to give 4.69 g (38% yield) of **1** as a yellow solid, mp 200° dec; ^1H-nmr (deuteriochloroform): 8.26 (s, 4H), 4.94 (s, 8H).

Anal. Calcd. for $C_{16}H_{12}Br_4N_2$: C, 34.82; H, 2.19; N, 5.08; Br, 57.91. Found: C, 34.56; H, 2.24; N, 5.02; Br, 58.30.

2,3,7,8-Tetrakis(azidomethyl)phenazine **4**.

A mixture of 1 g (1.81 mmoles) of **1** and 1 g (15.4 mmoles) of sodium azide in 200 ml of acetonitrile was heated under reflux for 2 hours. After filtration and evaporation of the solvent the crude material was extracted with dichloromethane. The organic layer was washed with water, dried and evaporated. The resulting solid was crystallized from 200 ml of 95% ethanol and dried in a dessicator (over phosphorus pentoxide) to give 0.55 g (76% yield) of **4** as a yellow-beige solid, mp 117°; ^1H nmr (deuteriochloro-

form): 8.27 (s, 4H); 4.72 (s, 8H); (dichloromethane): λ max nm (log ε) 263 (5.04), 375 (4.23).

Anal. Calcd. for $C_{16}H_{12}N_{14}$: C, 48.00; H, 3.02; N, 48.98. Found: C, 47.98; H, 3.04; N, 48.98.

2,8-Dimethyl-2,3,7,8-tetrahydro-1*H*,9*H*-bispyrrolo[3,4-*b*:3',4'-*i*]-phenazine **6**.

A mixture of 0.7 ml of a 40% aqueous solution of methylamine (8.13 mmoles) and 0.4 g (0.725 mmole) of **1** in 100 ml of THF was stirred at room temperature overnight in a closed flask. After evaporation of the THF the crude material was extracted with dichloromethane. The organic layer was washed with water dried and evaporated. The resulting solid (267 mg) was crystallized in 70 ml of toluene to give 123 mg (58% yield) of **6** as a beige solid, mp 250° dec; ^{1}H nmr (deuteriochloroform): 7.97 (s, 4H), 4.14 (s, 8H), 2.7 (s, 6H).

Anal. Calcd. for $C_{18}H_{18}N_4 \cdot 0.5\ H_2O$: C, 72.20; H, 6.39; N, 18.71. Found: C, 71.97; H, 6.09; N, 18.34.

2,8-Di-*n*-propyl-2,3,7,8-tetrahydro-1*H*,9*H*-bispyrrolo[3,4-*b*:3',-4'-*i*]phenazine **7**.

A mixture of 0.2 ml (2.43 mmoles) of *n*-propylamine and 0.2 g (0.362 mmole) of **1** in 75 ml of THF was stirred overnight, at room temperature, in a closed flask. After workup the crude product (206 mg) was crystallized in 25 ml of THF to give 70 mg (56% yield) of **7** as a greenish solid, mp 200° dec; ^{1}H-nmr (deuteriochloroform): 7.96 (s, 4H); 4.14 (s, 8H); 2.77 (t, J = 7.4 Hz, 4H); 1.69 (h, 4H); 1.02 (t, J = 7.4 Hz, 6H); uv (dichloromethane): λ max nm (log ε) 255 (5.11), 385 (4.26).

Anal. Calcd. for $C_{22}H_{26}N_4$: C, 76.27; H, 7.56; N, 16.17. Found: C, 76.49; H, 7.74; N, 16.38.

2,3,7,8-Tetrakis(acetylthiomethyl)phenazine **14**.

A mixture of 0.9 g (1.63 mmoles) of tetrabromide **1**, 1 ml of (14 mmoles) of thioacetic acid and 2 g (14.5 mmoles) of potassium carbonate in 40 ml of THF was refluxed for 3 hours. After workup the dark powder was extracted with dichloromethane and purified by filtration through a short column of alumina to give 0.69 g (80% yield) of phenazine **14** as an orange solid. Crystallization from toluene gave an analytical sample mp 203°; ^{1}H-nmr (deuteriochloroform): 8.13 (s, 4H); 4.38 (s, 8H); 2.36 (s, 12H); uv (dichloromethane): λ max nm (log ε) 270 (5.04), 387 (4.34).

Anal. Calcd. for $C_{24}H_{24}N_2S_4O_4$: C, 54.11; H, 4.54; N, 5.26. Found: C, 54.31; H, 4.56; N, 5.06.

2,3,7,8-Tetrakis(4-acetoxy-2-thiabutyl)phenazine **15**.

A mixture of 1.5 g (2.72 mmoles) of 2,3,7,8-tetrakis(bromomethyl)phenazine **1**, 1.4 g (11.6 mmoles) of 2-mercaptoethylacetate [22] and 1.8 g (13 mmoles) of potassium carbonate in 60 ml of dry THF was refluxed for 2 hours. After workup the crude product was heated in chloroform with decolorizing charcoal. After filtration the solvent was evaporated and the residue crystallized in 20 ml of methanol giving 1.17 g (61% yield) of **15** as a yellow solid which turned dark slowly, mp 91°; ^{1}H nmr (deuteriochloroform): 8.08 (s, 4H), 4.21 (s, 8H), 2.73 (t, 8H), 4.24 (t, 8H), 2.08 (s, 12H); uv (dichloromethane): λ max nm (log ε) 270 (5.18), 390 (4.38).

Anal. Calcd. for $C_{32}H_{40}N_2O_8S_4$: C, 54.22; H, 5.69; N, 3.95; O, 18.05; S, 18.09. Found: C, 53.96; H, 5.73; N, 3.84; O, 17.83; S, 17.81.

2,3,7,8-Tetrakis(4-hydroxy-2-thiabutyl)phenazine **16**.

One g (1.41 mmoles) of phenazine **15** and 0.9 g (6.51 mmoles) of potassium carbonate in 60 ml of methanol were refluxed for 3 hours. The mixture was quenched with 150 ml of water and the resulting precipitate was filtered, washed with water and dried giving 728 mg (95% yield) of **16** as a yellow-beige solid, which was used in the next step without further purification, mp 177°; ^{1}H nmr (pyridine-d_5): 8.52 (s, 4H), 4.62 (s, 8H), 3.05 (t, 8H), 4.19 (t, 8H).

2,3,7,8-Tetrakis(4-chloro-2-thiabutyl)phenazine **17**.

Four ml of thionyl chloride (54.8 mmoles) was added to a suspension of 0.5 g (0.925 ml) of the tetraalcohol **16** in 80 ml of chloroform. After refluxing the mixture for 2 hours, it was quenched by water. The organic layer was washed with water and dissolved in a minimum volume of chloroform. Adding methanol gave a precipitate which was filtered and crystallized in 20 ml of carbon tetrachloride to give 182 mg (32% yield) of **17** as a beige solid mp 105°.

Anal. Calcd. for $C_{24}H_{28}N_2Cl_4$: C, 46.91; H, 4.59; N, 4.56; S, 20.87; Cl, 23.07. Found: C, 46.91; H, 4.44; N, 4.50; S, 20.90; Cl, 22.89.

2,7-Bis(3-hydroxy-1-thiapropyl)phenazine **19**.

A mixture of 0.5 g of 2,7-dichlorophenazine **18** [19,20], 1.5 ml (21.4 mmoles) of 2-mercaptoethanol and 0.3 g (7.5 mmoles) of sodium hydroxide in 75 ml of 95% ethanol was heated to reflux overnight. The precipitate was filtrated, washed with water then with acetone and ether to give quantitatively a red-orange solid which was used without further purification; ^{1}H nmr (DMSO-d_6): 7.92 (d, J = 2 Hz, 2H), 7.76 (dd, 2H), 8.03 (d, J = 9.1 Hz, 2H), 3.30 (t, J = 6 Hz, 4H), 3.73 (q, 4H), 5.14 (t, J = 5.5 Hz, 2H).

2,7-Bis(3-Chloro-1-thiapropyl)phenazine **20**.

A solution of 0.67 g (2 mmoles) of the alcohol **19** and 3.5 ml (47.9 mmoles) of thionyl chloride in 100 ml of chloroform was refluxed for 4 hours. The mixture was quenched with water. The red solid obtained after work-up was dissolved in dichloromethane and the solution was filtrated through alumina and evaporated. The crude product was crystallized in 50 ml of carbon tetrachloride to give 338 mg (46% yield) of an orange solid, mp 150°; ^{1}H nmr (deuteriochloroform): 7.94 (d, J = 2.1 Hz, 2H), 2.67 (dd, 2H), 8.08 (d, J = 9.1 Hz, 2H), 3.51 (t, J = 8 Hz, 4H), 3.82 (t, 4H).

Anal. Calcd. for $C_{16}H_{14}N_2S_2Cl_2$: C, 52.03; H, 3.82; N, 7.59; Cl, 19.20; S, 17.36. Found: C, 51.73; H, 3.88; N, 7.77; Cl, 19.29; S, 17.30.

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