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SYNTHESIS OF N-ACRIDINYL AND N-QUINOLINYL DERIVATIVES OF RADIOPROTECTIVE AMINO-THIOLS

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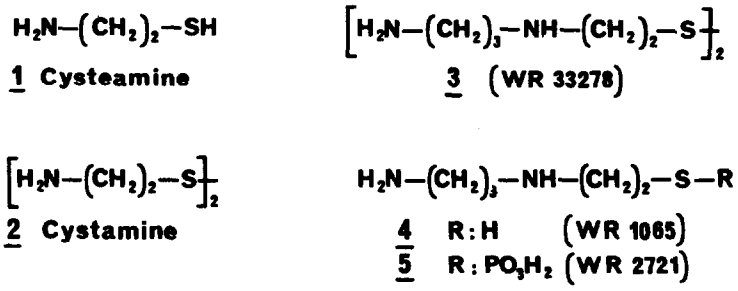
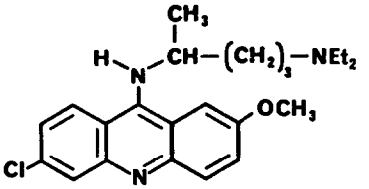
Abstract : A series of bifunctional molecules in which a heterocycle is linked to an aminothiol chain were synthesized. A new synthesis of N,N'-bis-(3-aminopropyl) cystamine (WR 33278) is described. Reaction of WR 33278 or analogues with the phenoxy derivatives of quinoline or acridine yielded the desired bifunctional molecules.

Aminothiols, the structures of which are derived from cysteamine 1, constitute a major class of radioprotective agents. Among them, (aminopropyl) aminoethyl phosphorothioïc acid 5 (WR-2721) is described as the most effective compound in the series (1). It protects mammalian cells against radiation. In vivo, it shows a good selectivity for normal cells in comparison to malignant ones (2, 3).

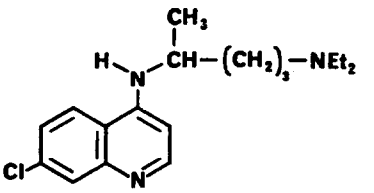


The mechanism of action of such radioprotective agents is still largely unclear. It now seems well established that deoxyribonucleic acid (DNA) is the major cellular target for ionizing radiation (4). The free thiols are suggested to be the active protective species. In vivo, they are generated by metabolic degradation (hydrolysis, reduction) of the protected derivatives (thioesters, disulfides), and are usually less toxic and more active. It has been suggested that the thiol acts by scavenging hydroxyl radicals generated from water close to the macromolecule or by chemical repair of the DNA

radicals formed by radiolysis. These two mechanisms require high concentrations of the radioprotector in the vicinity of DNA. However, most of the aminothiols and their derivatives, 1 to 5, exhibit low affinity for DNA (5). It should therefore be possible to increase the efficiency of the radioprotection by increasing the affinity of the drug for the macromolecule. In order to test this hypothesis we have prepared a series of molecules in which the radioprotective aminothiol is linked to an intercalating heterocycle possessing high affinity for DNA. As intercalators, we chose the 2-methoxy-6-chloro-9-aminoacridine and the 7-chloro-4-aminoquinoline. Both heterocycles have been incorporated into antimalarial drugs (quinacrine and chloroquine respectively). Their interaction with DNA has been extensively studied (6).



Quinacrine



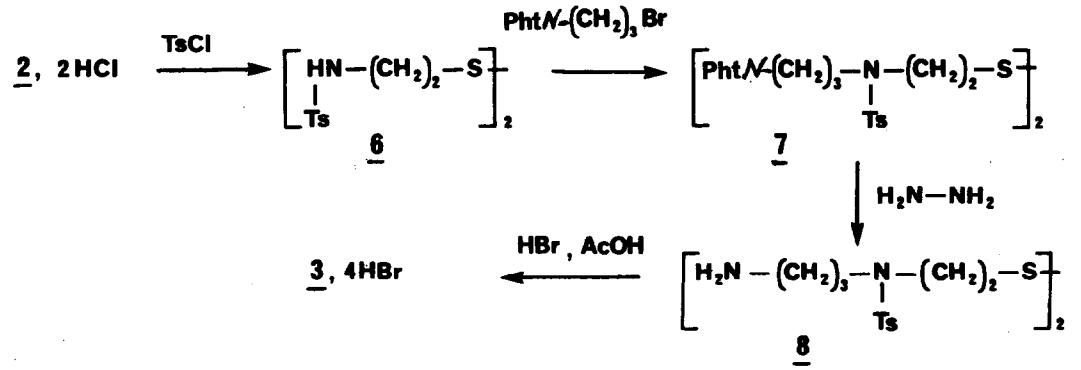
Chloroquine

The affinity constants of quinacrine and chloroquine for DNA are different (10^5 M^{-1} and 10^4 M^{-1} respectively). It should therefore be possible to establish a correlation between radioprotecting activity and affinity for DNA. Two series of compounds have been synthesized, depending of the nature and length of the aminothiol chain : i.e. cysteamine 1 and (aminopropyl) aminoethyl thiol 4. The thiol function was either protected as thioacetate, phosphorothioate and disulfide, or was in the free form. We report here the synthesis of two series of compounds : in the acridine series we describe disulfides 10, 11, thiol 16 and thioacetate 17 derivatives and in the quinoline series, the disulfides 20, 21, thiols 22, 23, thioacetate 24 and phosphorothioate 25 derivatives. The thiols and thioacetates derivatives were obtained from the corresponding disulfides 2 and 3. The long chain disulfide 3 was first prepared starting from commercial cystamine. The aromatic nucleophilic substitution of phenoxyacridine or quinoline by the aminodisulfides 2 or 3 gave the desired intermediates.

* Synthesis of N, N'-bis-(3-aminopropyl)cystamine 3

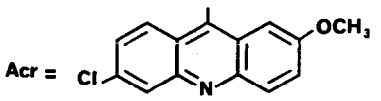
Disulfide 3, known as WR-33278, is usually prepared either by acidic hydrolysis of phosphorothioïc acid 5 and oxidation of the resulting thiol (5) or by reaction of ethylenesulfide with 1,3-diaminopropane followed by oxidation (7, 8). In the latter process, polyalkylation of the primary amino groups is a major problem. Precursor phosphorothioate 5 is prepared in a multistep procedure (9) with overall yields ranging from 19 to 33 %.

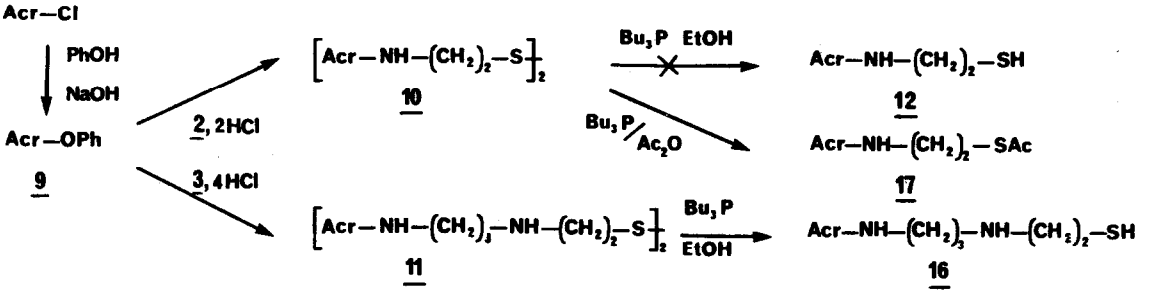
We describe here a direct synthesis of disulfide 3 starting from cystamine.



In the first step, tosylation was used both for protection and activation of the two aminogroups of cystamine 2. Alkylation with bromopropyl phthalimide followed by hydrazinolysis of the phthalimido group gave the desired aminopropyl aminoethyl thiol linkage with a very good yield. Acidic hydrolysis of the two p-toluenesulfonamido groups provided disulfide 3. The overall yield from cystamine is 37 %.

ACRIDINE SERIES





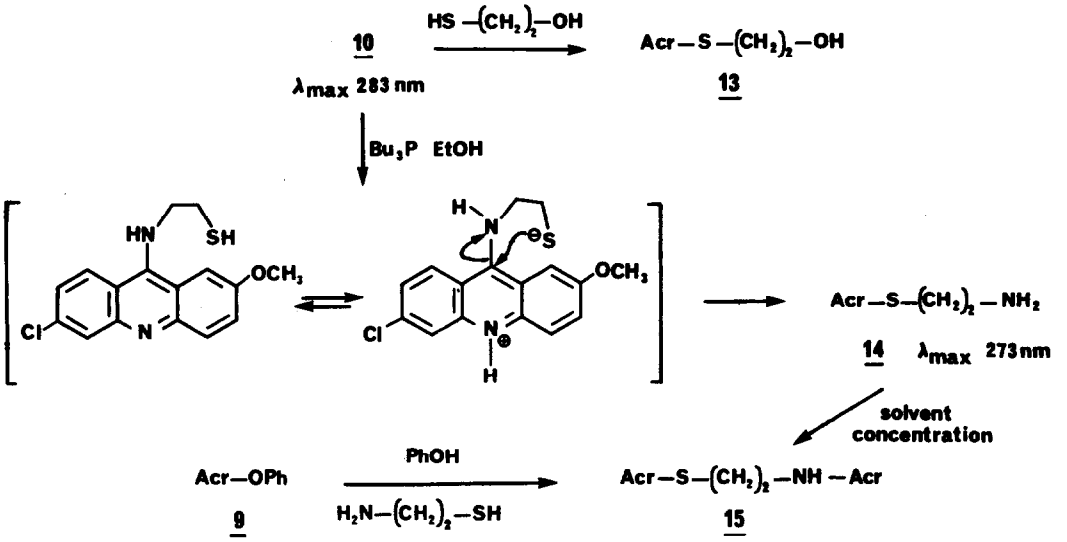
* Synthesis of disulfide derivatives 10 and 11

As mentioned above, the amino disulfide chain was introduced on the heterocycle by aromatic nucleophilic substitution. To improve the yield of this reaction we used the phenoxy derivative of acridine 9 and the hydrochloride form of the aminochain. As already described (10), the "in situ" protonation of the acridine nucleus increases the rate of the

substitution. Owing to problems of purification, the yields for 10 and 11 are about 58 %.

* Reduction to the thiols 12 and 16

A large number of reagents can be used to reduce disulfides to thiols (thiophenol, ß mercaptoethanol, Sn/HCl...). Reduction with an excess of thiol, which requires very mild conditions was attempted first. Unfortunately, reaction with ß mercaptoethanol resulted in substitution of the amino group in the 9-position by the thiol to give quantitatively the thioacridine 13. In an other attempt, reduction of the disulfide 10 with tributylphosphine did not give the thiol 12, as expected, but a mixture of compounds. It appears that the thiol 12 immediately rearranged to give the amine 14 by intramolecular process. Reduction and rearrangement were immediate as shown by HPLC. The chromatogram obtained two minutes after addition of the phosphine to the disulfide solution, indicated the formation of a single product with a maximum absorption at 273 nm, corresponding to a thioacridine derivative. This compound is very unstable and decomposes during removal of the solvent to give the N,S-bis-acridinyl derivative 15, identified by comparison with an authentic sample.



This intramolecular rearrangment was not observed with the long chain disulfide 11. Thiol 16 could be isolated by precipitation of the hydrochloride in 64 % yield. On the other hand, the reduction of disulfide 10 with tributylphosphine could be easily performed in acetic anhydride. Under these conditions, the reaction, as shown by HPLC, was complex due to a competition between internal rearrangment and acetylation of the thiol intermediate. After cooling of the solution, the desired thioacetate 17 precipitated, and

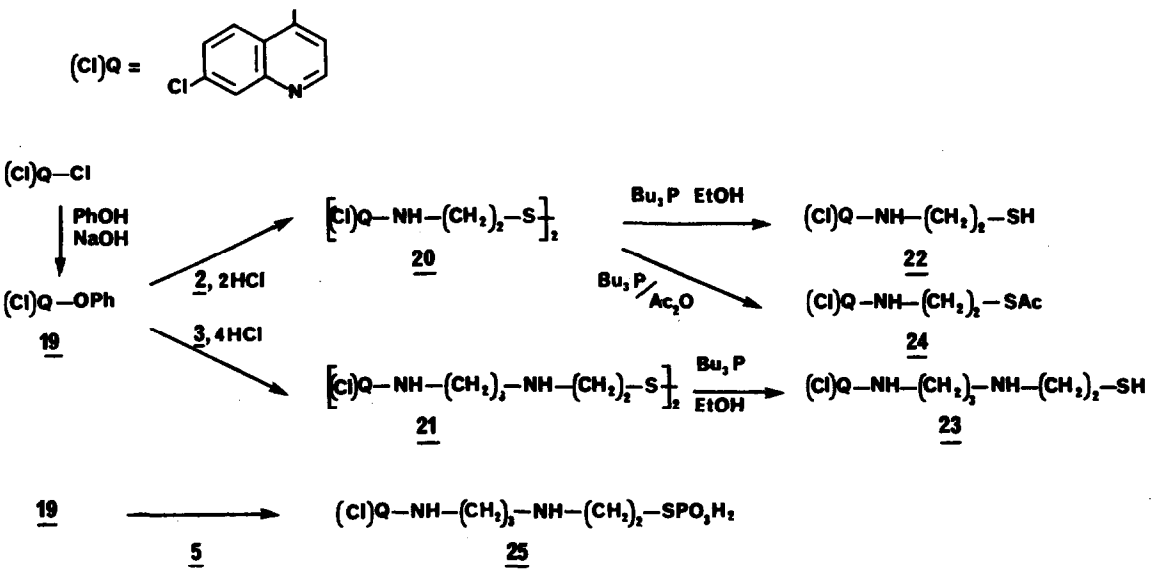
the latter could be obtained in a fairly pure state by recrystallization in acidic methanol in 50 % yield.

QUINOLINE SERIES

The same methods were used as described for the acridine series.

* Synthesis of disulfide derivatives 20 and 21

Substitution of the 4-phenoxyquinoline 19 with amino disulfides 2 and 3 (as the hydrochlorides) required a longer time of reaction (40 hours instead of 5 fours for the acridine series). The yields were better, respectively 85 % and 62 %.



* Synthesis of thiols 22 and 23

Reduction of disulfides with tributylphosphine in methanol gave the desired thiols 22 and 23 in about 75 % yield. Neither intra- nor intermolecular rearrangement were observed.

* Synthesis of thioacetate 24

The thioacetate 24 was obtained in 85 % yield after reduction of the disulfide 20 in acetic anhydride, extraction and crystallization in ethanolic hydrochloric acid. It may be noticed that the yield is much better than in the acridine series, without any competing reaction.

* Synthesis of the phosphorothioate 25

The aromatic substitution was carried out under the conditions described above for the synthesis of disulfide derivatives (phenol, 80°C). The reaction was followed by TLC. After 6 hours of heating, the reaction was complete. THe product precipitated by adding ether to the solution. The yield was 48 % after crystallization from water-ethanol mixture.

CONCLUSION

The differences of reactivity between the 9-position of acridine and 4-position of quinoline reflect the well-known effect of fusion a second benzene ring (11). Nevertheless, the rapid intra or intermolecular substitution of the 9-amino group of acridine by thiols is unexpected. We are currently studying the mechanism and rate of the nucleophilic substitution.

The radioprotecting properties of the molecules described here on nucleosides have been published in a preliminary paper (12). The compounds were found to protect thymidine by acting as scavengers for the water radiolysis species and as hydrogen donors. We are now studying their action on DNA and oligonucleotides.

EXPERIMENTAL SECTION

General : Unless mentioned otherwise ^{1}HNMR spectra were recorded on a Bruker WP60 (60 MHz). Chemical shifts are reported in ppm (δ) relative to hexamethyldisiloxane as internal standard. UV spetra were recorded on a Perkin Lambda 15. IR spectra were recorded on a Perkin-Elmer 237. Melting points are uncorrected. Reversed-phase HPLC was performed using a μ-Bondapak C18 analytical column (Waters Associates) equipped with an automated gradient controller and two M510 pumps (Waters Associates). The effluent was analyzed by a Waters 990 photodiode array detector controlled by a NEC APC IV Computer. A linear gradient of solvent was used from 0 to 100 % methanol in water pH 2,5 (phosphoric acid) during 10 min with a 2 mL/min flow rate. Elemental analysis was performed by "Service Central de Microanalyse du CNRS" (France).

* **N,N'-bis-(paratoluenesulfonyl)cystamine 6** : Cystamine hydrochloride (5g, 22.2 mmol) dissolved in aqueous sodium hydroxide (3.6 g, 90 mmol in 50 mL) was cooled near 0°C. Paratoluenesulfonylchloride (10 g, 52.4 mmol) was solubilised in diethylether (10 mL), diluted with water (10 mL), cooled near 0°C and added dropwise to cystamine solution under vigourous stirring. Reaction proceeded 1 hour at 0°C then 2 hours at room temperature. The white precipitate was filtrated and solubilized into 2N sodium hydroxide (100 mL). After 12 hours stirring, the solution was neutralized with 12N hydrochloric acid and extracted with

methylene chloride. The organic solvent was dried on magnesium sulfate, filtered, then evaporated to dryness. The resulting oil was diluted with a minimum amount of chloroform, addition of hexane afforded 6 as white crystals (9.2 g, 90 % yield). mp 77-78°C ; ir(KBr) 3280, 3090, 3060, 2990, 2950, 2890, 1610, 1505, 1450, 1360, 1340, 1160, 1040, 945 cm^{-1} ; UV(EtOH) λ_{max} (ε) 278 (23000), 202 (30700) nm ; ^{1}Hnmr ($CDCl_3$) δ 7.70-7.25 (8H, q, 2 x TsH), 3.30 (4H, t, 2 x NCH_2), 2.80 (4H, t, 2 x SCH_2), 2.40 (6H, s, 2 x $TsCH_3$) ; Anal. Calcd for $C_{18}H_{24}N_2O_4S_4$: C, 46.93 ; H, 5.25 ; N, 6.08. Found : C, 46.76; H, 5.34 ; N, 6.30.

* **N,N'-bis-(paratoluenesulfonyl)-N,N'-bis(3-phtalimidopropyl)cystamine** 7 : A mixture of 6 (9.2 g, 20 mmol), 3-bromopropyl phtalimide (21.5 g, 80 mmol), potassium carbonate (15 g, 105 mmol) and a catalytic amount of tetrabutylammonium iodide (0.2 g) dissolved in dry DMF (50 mL) was stirred at 80°C under inert atmosphere for 2 days. The solution was cooled, filtered and evaporated in vacuo. Separation over column chromatography (methylene chloride as eluent) and crystallization from chloroforme-hexane mixture afforded 7 as a white solid (14 g, 84 % yield). mp 137-139°C ; ir(KBr) 2950, 1780, 1720, 1610, 1410, 1350, 1165 cm^{-1} ; ^{1}Hnmr ($CDCl_3$) δ 7.70- 7.15 (16H, m, 2 x TsH and 2 x Pht-H), 3.75-2.80 (16H, m, 2 x SCH_2 and 6 x NCH_2), 2.35 (6H, s, 2 x $TsCH_3$), 1.90 (4H, m, 2 x CH_2) ; Anal. Calcd for $C_{40}H_{42}N_4O_8S_4$: C, 57.53 ; H, 5.07 ; N, 6.71. Found : C, 57.29 ; H, 4.97 ; N, 6.63.

* **N,N'-bis(paratoluenesulfonyl)-N,N'-bis(3-aminopropyl)cystamine** 8 : To a suspension of 7 (12 g, 14.4 mmol) in ethanol warmed at 80°C was added hydrazine hydrate in large excess (8 mL, 168 mmol). The solution was stirred at 80°C for 10 hours and then cooled at room temperature, filtered and evaporated. The residue was diluted with saturated sodium chloride (100 mL) and extracted with methylene chloride. Organic solution was dried over magnesium sulfate, filtered and evaporated to give 8 as an oil (6.6 g, 80 %).
ir(NaCl) 3400, 2950, 2890, 1610, 1460, 1345, 1165, 1100, 825, 745 cm^{-1} ; ^{1}Hnmr (CD_3OD) δ 7.50 (8H, m, 2 x TsH), 3.10 (16H, m, 2 x SCH_2 and 6 x N-CH_2), 2.40 (6H, S, 2 x $TsCH_3$), 1.90 (4H, m, 2 x CH_2).

* **N,N'-bis(3-aminopropyl)cystamine tetrahydrobromide** 3 : Compound 8 (6.6 g, 11.5 mmol) was stirred in 20 % hydrogen bromide in acetic acid solution (40 mL) containing a catalytic amount of phenol (0.1 mL). The reaction mixture was kept at 80°C for 5 hours and then cooled at room temperature. Hydrobromide salt of 3 precipitated during the reaction. It was filtered and crystallized from methanol-water (15/1). mp 163°C (dec.) ; ir(KBr) 2950, 2820, 2790, 2480, 2420, 1450, 1410 cm^{-1} ; ^{1}Hnmr (D_2O) δ 3.30 (16H, m, 2 x SCH_2 and 6 x NCH_2), 2.15 (4H, m, 2 x CH_2) ; Anal. Calcd for $C_{10}H_{30}N_4S_2Br_4$: C, 20.35 ; H, 5.12 ; N, 9.49. Found : C, 20.74 ; H, 5.27 ; N, 9.32.

* **7-chloro-2-methoxy-9-phenoxyacridine** 9 was prepared as described in the literature (13). The crude product was purified by crystallizing from acetone. mp : 153-155° Hnmr ($CDCl_3$) 8.15-7.80 (3H, m), 7.45-6.75 (8H, m), 3.75 (3H, s, Acr-OCH_3) ; ms (relative intensity)

m/e : 335 (M^+, 100), 320 (39), 285 (51), 258 (32).

* **N,N'-bis-(7-chloro-2-methoxy-9-acridinyl)cystamine 10** : Phenoxyacridine 9 (1.2 g, 3.57 mmol) and cystamine hydrochloride (0.34 g, 1.52 mmol) were stirred at 80°C in phenol (8 mL) for 5 hours. The solution was then poured into 2N sodium hydroxide (100 mL). Compound 10 was purified as the free base by crystallizing from acetone-water (8/1) mixture (0.56 g, 58 %). The hydrochloride was obtained by bubbling dry hydrogen chloride into a solution of 10 in acetone (150 mL). mp 180°C (dec.) ; ir(KBr) 3430, 2950, 1650, 1575, 1480, 1440, 1355, 1270, 1250, 1040, 940, 830 cm^{-1} ; UV(EtOH) λ_{max} (ε) 414 (13500), 360 (7900), 342 (5300), 268 (110000), 227 (50400) nm ; ^{1}Hnmr (DMSO-d_6) δ8.20 (2H, d, 2 x AcrC_8-H), 7.90-7.15 (10H, m, 2 x Acr-H), 6.70 (2H, S, 2 x NH), 3.80 (6H, S, 2 x Acr-OCH_3 and 4H, m, 2 x S-CH_2) ; Anal. Calcd for $C_{32}H_{28}N_4O_2S_2Cl_2$: C, 60.47 ; H, 4.44 ; N, 8.81. Found : C, 60.75 ; H, 4.49; N, 8.43.

* **Reduction of disulfide 10 with 2-hydroxyethanethiol. Obtention of 6-chloro-9-[(hydroxy-2-ethyl)thio]-2-methoxyacridine 13** : To a solution of disulfide 10 (0.03 g, 0.05 mmol) in ethanol (5 mL) was added a large excess of 2-hydroxyethanethiol (0.03 mL, 0.5 mmol). The solution was kept 5 hours at room temperature in the dark. Compound 13 precipitated progressively. It was crystallized from ethanol in a quantitative yield. ir(KBr) 3200, 2970, 2850, 1640, 1480, 1430 cm^{-1} ; ^{1}Hnmr (DMSO-d_6) δ8.70 (1H, d, Acr-C_8H), 8.15-7.60 (5H, m, AcrH), 4.70 (1H, S, OH), 3.95 (3H, S, Acr-OCH_3), 3.05 (4H, m, SCH_2 and CH_2-OH) ; ms (relative intensity) m/e : 319 (M^+, 100), 274 ($AcrS^+$, 43).

* **N,S-bis-(7-chloro-2-methoxy-9-acridinyl)cysteamine 15** : Cysteamine hydrochloride (0.2 g, 1.5 mmol) and phenoxyacridine 9 (1.2 g, 3.6 mmol) were stirred at 80°C in phenol (6 mL) for 3 hours. Compound 15 was precipitated by pouring the mixture into 2N-Sodium hydroxide and crystallized from acetone (0.62 g, 72 % yield). mp 200°C (dec.) ; ir(KBr) 3430, 2950, 2880, 1620, 1570, 1550, 1460, 1380, 1060 cm^{-1} ; UV(EtOH) λ_{max} (ε) 401 (8200), 361 (7200), 266 (90100), 226 (32300) nm ; ^{1}Hnmr (TFA-d) δ 8.20 (1H, d, AcrC_8-H), 7.90-6.55 (11H, m, 2 x Acr-H), 4.20 (2H, m, NCH_2), 3.65 (2H, m, SCH_2), 3.55 and 3.40 (3H, S, AcrOCH_3) ; Anal. Calcd for $C_{30}H_{23}N_3O_2SCl_2$, $1.5H_2O$: C, 61.33 ; H, 4.46 ; N, 7.15. Found : C, 61.33 ; H, 4.26 ; N, 6.79.

* **N,N'-bis-[3-(-7-chloro-2-methoxy-9-acridinyl)aminopropyl]cysteamine tetrahydrochloride 11** : A mixture of 3 tetrahydrobromide (0.5g, 0.85 mmol), phenoxyacridine 9 (0.9 g, 2.6 mmol) and triethylamine (0.24 mL, 1.7 mmol) in phenol (4 mL) was stirred at 80°C for 8 hours. The yellow precipitate obtained by pouring the solution in 2N-sodium hydroxide, was washed successively with water and dry diethylether. Tetrahydrochloride form was isolated by bubbling dry hydrogen chloride into an ethanolic solution of 11 (0.45 g, 59 % yield). mp 170°C (dec.) ; ir(KBr) 3390, 3100, 1620, 1585, 1450, 1240, 1090, 1035, 940 cm^{-1} ; UV(EtOH) λ_{max} (ε) 446 (14900), 424 (16000), 282 (81500), 222 (37300) nm ; ^{1}Hnmr

(300 MHz, D_2O) δ7.96 (2H, d, J = 9.3 Hz, 2 x $AcrC_8$-H), 7.45 (4H, S, 2 x $AcrC_3$-H and 2 x $AcrC_4$-H), 7.35 (2H, d, J = 1.9 Hz, 2 x $AcrC_5$-H), 7.30 (2H, dd, J = 1.9 Hz and 9.3 Hz, 2 x $AcrC_7$-H), 7.22 (2H, S, 2 x $AcrNHCH_2$), 4.02 (4H, t, 2 x $AcrNHCH_2$), 3.92 (6H, S, 2 x $AcrOCH_3$), 3.44 (4H, t, 2 x CH_2CH_2S), 3.27 (4H, t, 2 x $AcrNHCH_2CH_2CH_2$), 3.17 (4H, t, 2 x CH_2S), 2.33 (4H, m, 2 x CH_2-CH_2-CH_2) ; Anal. Calcd for $C_{38}H_{46}N_6O_2Cl_6S_2$, $5H_2O$: C, 46.30 ; H, 5.73 ; N, 8.53. Found : C, 46.16 ; H, 5.63 ; N, 8.51.

* **N-[3-(7-chloro-2-methoxy-9-acridinyl)aminopropyl] cysteamine dihydrochloride 16** : To a suspension of disulfide 11 hydrochloride (0.2 g, 0.22 mmol) in ethanol (200 mL) was added the tri-n-butylphosphine (0.5 mL, 2 mmol). After 6 hours stirring the clear solution was filtered and petroleum ether was added to the filtrate. The solution was kept at -20°C overnight. The yellow precipitate was filtered, washed with petroleum ether and dried. The purity was checked by HPLC. The yield was 55 % of an analytically pure product (0.19 g). mp 167°C (dec.) ; ir(KBr) 3200, 1625, 1585, 1500, 1235, 1090, 1025, 930 cm^{-1} ; UV(EtOH 95 %) λ_{max} (ε) 421 (8500), 342 (3500), 280 (44000), 267 (47000), 225 (28800) nm ; ^{1}Hnmr (DMSO-d_6) 9.90 (S, 1H, NH), 9.20 (S, 1H, NH), 8.60 (d, 1H, J = 9.0 Hz, $AcrC_8$-H), 7.45-8.55 (m, 10H, Acr-H), 4.25 (m, 2H, N-CH_2), 4.00 (m, 3H, Acr-OCH_3), 2.20-3.00 (m, -CH_2-) ; ms (FAB+) m/e 377 (M^+, Cl^{37}), 375 (M^+, Cl^{35}) ; Anal. Calcd for $C_{19}H_{24}N_3OCl_3S$, $1H_2O$: C, 48.88; H, 5.61 ; N, 9.00. Found : C, 48.88 ; H, 5.75 ; N, 8.80.

* **S-acetyl-N-(7-chloro-2-methoxy-9-acridinyl)cysteamine hydrochloride 17** : To a suspension of disulfide 10 (0.2 g, 0.3 mmol) in acetic anhydride (100 mL) was added a large excess of tri-n-butylphosphine (1 mL, 4 mmol). The solution warmed at 60°C and was stirred until complete dissolution of the starting disulfide. After filtration on celite, the solution was kept at -20°C overnight. The yellow precipitate was filtered, washed with acetic anhydride with an aqueous solution of sodium carbonate. The crude product was crystallized in acidic methanol to give the hydrochloride with 50 % yield. mp 244-245 °C ; ir(KBr) 3250, 2650, 1690, 1630, 1590, 1560, 1500, 1480, 1450, 1395, 1345, 1275, 1250, 1185, 1120, 1090, 1030, 930 cm^{-1} ; UV (EtOH 95 %) λ_{max} (ε) 413 (7700), 359 (4600), 341 (3300), 268 (57500), 226 (28000) nm ; ^{1}Hnmr (DMSO-d_6, 300 MHz) δ 9.70 (S, 1H, HN), 8.55 (d, 1H, J = 9.3 Hz, $AcrC_8$-H), 7.90-7.99 (m, 3H, Acr-H), 7.70 (m, 1H, Acr-H), 7.52 (m, 1H, Acr-H), 4.24 (t, 2H, N-CH_2), 3.97 (S, 3H, Acr-OCH_3), 3.40 (t, 2H, S-CH_2), 2.29 (S, 3H, $COCH_3$) ; ms (FAB+) m/e 362 (M^+, Cl^{37}), 360 (M^+, Cl^{35}) ; Anal. Calcd for $C_{18}H_{18}N_2O_2SCl$, 1 MeOH : C, 53.15 ; H, 5.11 ; N, 6.49. Found : C, 52.65; H, 5.11 ; N, 6.49.

* **7-chloro-4-phenoxyquinoline hydrochloride 19** : 4,7-Dichloroquinoline (5 g, 25 mmol) was added to a mixture of sodium hydroxide (1.5 g, 38 mmol) and freshly distilled phenol (15 mL) warmed at 100°C. The solution was kept at 100°C for 7 hours under 2N sodium hydroxide (100 mL). The phenoxyquinoline 19 was extracted with chloroform, purified by column chromatography on silica gel (methylene chloride as eluant). Evaporation under reduced pressure gave the desired compound as an oil (5.9 g, 92 % yield). The hydrochloride

derivative was obtained after crystallization from a methanolic solution of hydrochloric acid. mp (hydrochloride) 195-198°C (Lit. (14) 207.5-210°C) ; ^{1}Hnmr (free base in CD_3OD) δ8.60(1H, d, J = 5.6 Hz, QC_2-H), 8.35 (1H, d, J = 9.0 Hz, QC_5-H), 7.95 (1H, d, J = 1.7 Hz, QC_8-H), 7.65-7.10 (6H, m, QC_6-H and Ph-H), 6.55 (1H, d, J = 5.6 Hz, Qc_3-H).

* **N,N'-bis-(7-chloro-4-quinolyl)cystamine dihydrochloride 20** : A mixture of cystamine hydrochloride (1.5 g, 6.7 mmol) and 7-chloro-4- phenoxyquinoline 19 (4.5 g, 17.6 mmol) was stirred for 40 hours in phenol (4 mL) warmed at 90°C under inert atmosphere and then poured into 2N sodium hydroxide (100 mL). Compound 20, which precipitated, was filtered off and crystallized from methanolic hydrochloric acid (3.1 g, 85 % yield).
mp 130°C (dec.) ; ir(KBr) 3250, 2850, 1625, 1600, 1470, 1225, 810 cm^{-1} ; UV(EtOH) λ_{max} (ϵ) 243 (23000), 331 (26000), 255 (29600), 219 (64600) nm ; ^{1}Hnmr (CF_3CO_2D) δ 7.85 (2H, d, J = 7.4 Hz, 2 x QC_2-H), 7.70 (2H, d, J = 9.2 Hz, 2 x QC_5-H), 7.45 (2H, S, 2 x QC_8-H), 7.25 (2H, d, J = 9.2 Hz, 2 x QC_6-H), 6.45 (2H, d, J = 7.4 Hz, 2 x QC_3-H), 3.65 (4H, t, 2 x NCH_2), 2.70 (4H, t, 2 x SCH_2) ; Anal. Calcd for $C_{22}H_{22}N_4S_2Cl_4$, 1.5 H_2O : C, 45.92 ; H, 4.38 ; N, 9.74. Found : C, 45.88 ; H, 4.36 ; N, 9.68.

* **N,N'-bis-[3-(7-chloro-4-quinolyl)aminopropyl] cystamine tetrahydrochloride 21** : Compound 3 tetrahydrobromide (5 g, 3.4 mmol) was solubilized in hot phenol (6 mL) by adding triethylamine (1.9 mL, 13.6 mmol) and 7-chloro-4-phenoxyquinoline 19 (2 g, 7.8 mmol). The mixture was stirred at 90°C for 40 hours and then poured into 5N sodium hydroxide. After extraction with methylene chloride and evaporation of the solvent the resulting oil was purified by column chromatography on silica gel (elution with a methylene chloride-methanol mixture). The residue obtained after evaporation was dissolved in ethanol and compound 21 was isolated as the hydrochloride by bubbling dry hydrogen chloride through the solution. Recrystallization from ethanol-water (20/1) mixture afforded pure disulfide 21 (1.53 g, 62 % yield). mp 220°C (dec.) ; ir(KBr) 3400, 2750, 1615, 1590, 1450, 1360, 1220 cm^{-1} ; UV(EtOH) λ_{max} (ϵ) 343 (31300), 330 (31500), 257 (33500), 236 (35500), 221 (66600) ; ^{1}Hnmr (D_2O)δ8.40 (2H, d, J = 7.2 Hz, 2 x QC_2-H), 8.10 (2H, d, J = 9.3 Hz, 2 x QC_5-H), 7.80 (2H, S, 2 x QC_8-H), 7.60 (2H, d, J = 9.3 Hz, 2 x QC_6-H), 6.90 (2H, d, J = 7.2 Hz, 2 x QC_3-H), 3.50 (16H, m, 2 x SCH_2 and 6 x NCH_2), 2.30 (4H, m, 2 x CH_2) ; Anal. Calcd for $C_{28}H_{38}N_6S_2Cl_6$, $3H_2O$: C, 42.60; H, 5.62 ; N, 10.64. Found : C, 42.85 ; H, 5.51 ; N, 10.58.

* **N-(7-chloro-4-quinolyl)cysteamine hydrochloride 22** : To disulfide 20 (1 g, 1.8 mmol) dissolved in methanol (30 mL) was added an excess of tri-n-butylphosphine (0.9 mL, 3.6 mmol). The solution was kept at room temperature in the dark for 30 min. After concentration of the solvent under reduced pressure, thiol 22 was crystallized as the hydrochloride by addition of diethylether (0.73 g, 75 % yield). mp 212-215°C ; ir(KBr) 3250, 3025, 2750, 1625, 1600, 1565, 1460, 1225 cm^{-1} ; UV(EtOH) λ_{max} (ϵ) 344 (15500), 331 (15600), 256 (29600), 220 (33300) nm ; ^{1}Hnmr (D_2O) δ 8.30 (1H, d, J = 7.2 Hz, QC_2-H),

7.95 (1H, d, J = 9.0 Hz, QC_5-H), 7.70 (1H, d, J = 1.7 Hz, QC_8-H), 7.50 (1H, dd, J = 1.7 Hz and 9.0 Hz, QC_6-H),6.80 (1H, d, J = 7.2 Hz, QC_3-H), 3.80 (2H, t, NCH_2), 2.90 (2H, t, SCH_2) ; Anal. Calcd for $C_{11}H_{12}N_2SCl_2$, 0.5 H_2O : C, 46.49 ; H, 4.61 ; N, 9.86 ; S, 11.28. Found : C, 46.19 ; H, 4.83 ; N, 9.76 ; S, 11.23.

* **N-[3-(7-chloro-4-quinolyl)aminopropyl] cysteamine dihydrochloride 23** : Thiol 23 was prepared as described above for 22, from disulfide 21 (1 g, 1.4 mmol) and tri-n-butylphosphine (0.7 mL, 2.8 mmol). Compound 23 was isolated as the hydrochloride in 75 % yield (0.77 g). mp 75-77°C ; ir(KBr) 3250, 2960, 2800, 2490, 1620, 1580, 1460, 1370, 1220 cm^{-1} ; UV(EtOH) λ_{max} (ε) 340 (6900), 330 (7900), 256 (9900), 220 (20300) nm; ^{1}Hnmr (D_2O) δ8.35 (1H, d, J = 7.1 Hz, QC_2-H), 8.05 (1H, d, J = 8.6 Hz, QC_5-H) 7.70 (1H, S, QC_8-H), 7.55 (1H, d, J = 8.6 Hz, QC_6-H), 6.85 (1H, d, J = 7.1 Hz, QC_3-H), 3.95-2.70 (8H, m, 3 x N-CH_2 and SCH_2), 2.25 (2H, m, CH_2). Anal. Calcd for $C_{14}H_{20}N_3SCl_3$, $2H_2O$: C, 41.54 ; H, 5.98 ; N, 10.38. Found : C, 41.03 ; H, 6.03 ; N, 9.91.

* **S-acetyl-N-(7-chloro-4-quinolyl)cysteamine hydrochloride 24** : A mixture of disulfide 20 (1g, 1.8 mmol), triethylamine (1 mL, 7.2 mmol) and tri- n-butylphosphine (2.3 mL, 9 mmol) was stirred for 30 min at room temperature. Acetic anhydride (16 mL) and 4-(dimethylamino)pyridine (0.2 g, 1.8 mmol) were added and the solution was kept 2 days at room temperature in the dark. After evaporation of the solvent, the resulting oil was diluted with aqueous sodium bicarbonate (50 mL) and extracted with chloroform. Thioester 24 obtained after evaporation of the organic solvent was purified as the hydrochloride by crystallization from ethanolichydrochloric acid-ether solution (0.95 g, 83 % yield).
mp 220°C (dec.) ; ir(KBr) 3200, 3030, 2750, 1690, 1610, 1550, 1450, 1220, 1140 cm^{-1} ; UV(EtOH) λ_{max} (ε) 330 (12400), 253 (15900), 220 (32900) nm ; ^{1}Hnmr (D_2O) δ 8.30 (1H, d, J = 7.1 Hz, QC_2-H), 7.95 (1H, d, J = 8.9 Hz, QC_5-H), 7.70 (1H, S, QC_8-H), 7.55 (1H, d, J = 8.9 Hz, QC_6-H), 6.90 (1H, d, J = 7.1 Hz, QC_3-H), 3.80 (2H, t, NCH_2), 3.25 (2H, t, SCH_2), 2.40 (3H, S, $COCH_3$). Anal. Calcd $C_{13}H_{14}N_2OSCl_2$, $0.5H_2O$: C, 47.86 ; H, 4.63 ; N, 8.59. Found : C, 48.28 ; H, 4.57 ; N, 8.48.

* **S-[2-(3-((7-chloro-4-quinolyl)amino)propyl)aminoethyl] phosphorothioate 25** : S- 2-(3-aminopropyl)aminoethyl phosphorothioate 5 (0.5 g, 2.3 mmol) and 7-chloro-4-phenoxyquinoline hydrochloride 19 (1 g, 3.4 mmol) were stirred in freshly distilled phenol (3 mL) for 6 hours at 80°C under an inert atmosphere. Compound 25 was precipitated by pouring the solution into dry diethylether and crystallized in hot ethanolic hydrochloric acid solution. A second crystallization from ethanol-water mixture (10/1) afforded 25 as the hydrochloride in 48 % yield (0.46 g). mp 230°C (dec.) ; ir(KBr) 3350, 2950, 2725, 1595, 1455, 1420, 1290, 1205, 1170, 1100 cm^{-1} ; UV(EtOH) λ_{max} (ε) 323 (8000), 309 (9800), 230 (37000) ,m ; ^{1}Hnmr (D_2O) δ8.70 (1H,d, J = 6.7 Hz, QC_2-H), 8.10 (1H, d, J = 9.2 Hz, QC_5-H), 7.95 (1H, S, QC_8-H), 7.75-7.60 (2H, m, QC_6-H and QC_3-H), 3.80-2.95 (8H, m, SCH_2 and 3 x NCH_2), 2.20 (2H, m, CH_2). Anal. Calcd for $C_{14}H_{19}N_3O_3SPCl$, 1HCl, $2H_2O$: C,

37.51 ; H, 5.40 ; N, 9.37. Found : C, 37.79 ; H, 5.56 ; N, 9.60.

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