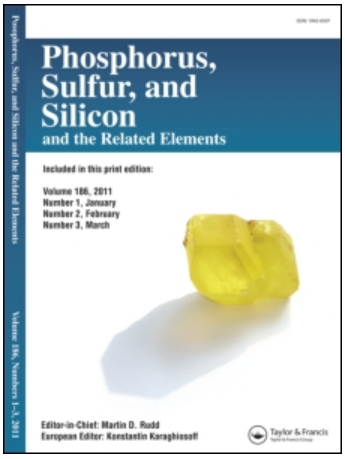


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# SYNTHESIS OF SOME NOVEL 1-AZAPHENOTHIAZINES AND THEIR MESOIONICS AS ANALOGUES OF POTENT CNS-DEPRESSANTS

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# SYNTHESIS OF SOME NOVEL 1-AZAPHENOTHIAZINES AND THEIR MESOIONICS AS ANALOGUES OF POTENT CNS-DEPRESSANTS

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1-Azaphenothiazine derivatives were synthesized by the condensation of the zinc salt of substituted 2-aminobenzenethiols and 2-chloro-3, 5-dinitropyridines. Mesoionic compounds, viz. substituted 1-hydroxy-2-chloroacetyl-, piperidinoacetyl-, and piperazinoacetyl-4-nitro-6-thia-10*b*-aza-2*a*-azoniaaceanthrylene hydroxide inner salts and substituted 1-hydroxy-4-nitro-6-thia-10*b*-aza-2*a*-azoniaaceanthrylene hydroxide inner salts were prepared. The synthesized compounds were characterized by elemental analyses, IR and $^1$H NMR and were screened for antimicrobical activity.

*Keywords:* 1-Azaphenothiazines or pyrido [3,2-*b*][1,4] benzothiazines; mesoionic compounds; 1-hydroxy-2-chloroacetyl-, piperidinoacetyl-, piperazinoacetyl-4-nitro-6-thia-10*b*-aza-2*a*-azoniaaceanthrylene hydroxide inner salts; 1-hydroxy-4-nitro-6-thia-10*b*-aza-2*a*-azoniaaceanthrylene hydroxide inner salts; IR; $^1$H NMR analyses; antimicrobial activity

## INTRODUCTION

1-Azaphenothiazines are well known to possess various biological activities, viz., neuroleptic, antitumor, antileukemic, local anesthetic, antiemetic etc. Prothiopendyl, an aminoalkylated 1-azaphenothiazine, is an effective CNS-depressant[1], and its potency has been reported to be enhanced by appropriate side chain alteration. 1-Azaphenothiazine bearing a side chain with a piperazine nucleus has been reported to be ten times as potent as prothiopendyl[2]. Other 1-azaphenothiazines were also reported to possess CNS depressant activity[3,4]. In view of the above results, an effort has been made to further investigate the biological potential of this heterocyclic system.

*Corresponding author.

Mesoionics were obtained as result of an unusual ring transformation while an attempt for chloroacetylation of 1-azaphenothiazine was effected. These compounds were further converted into different derivatives with the aim of obtaining new agents with substantial activities.

## RESULTS AND DISCUSSION

2-Amino-substituted phenyl-2′-(3′,5′-dinitro)pyridyl sulphide **II** was obtained upon treatment of a zinc salt of the 2-amino-substituted benzenethiol **I** with 2-chloro-3,5-dinitropyridine in anhydrous sodium acetate and absolute ethanol. Compound **II**, on treatment with acetic anhydride in pyridine, gave 2-acetylamino-substituted phenyl-2′-(3′,5′-dinitro)pyridyl sulphide **III**. Compound **III** was converted into 10-acetyl-substituted-3-nitro-1-azaphenothiazine **IV** and into 10*H*-substituted-3-nitro-1-azaphenothiazine **V** by treatment with acetone in presence of 1.0 and 2.2-mole(s) of potassium hydroxide, respectively. Compound **V** on treatment with $H_2O_2$ (30%), oxidized to 10*H*-substituted-3-nitro-1-azaphenothiazine-5-oxide **VI**.

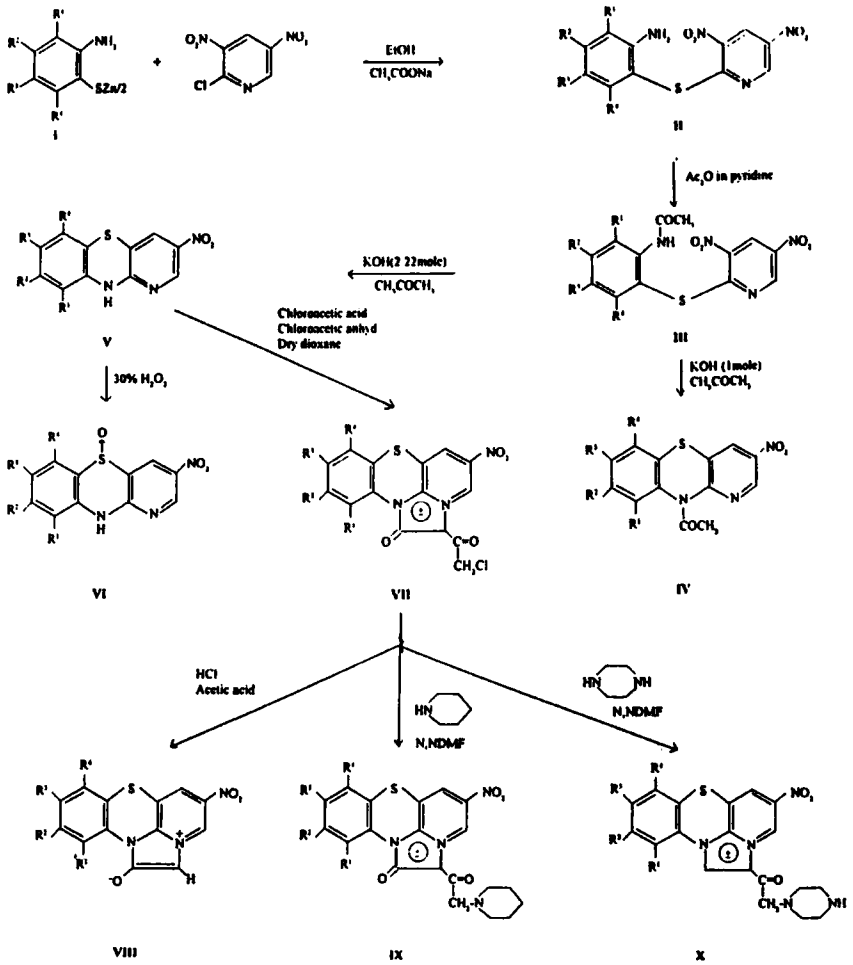
Chloroacetylation of **V** with chloroacetic anhydride in presence of chloroacetic acid gave substituted-1-hydroxy-2-chloroacetyl-4-nitro-6-thia-10*b*-aza-2*a*-azoniaaceanthrylene hydroxide inner salt **VII**, instead of the simple 10-chloroacetyl-1-azaphenothiazine. The hydrolysis of **VII** in acidic medium afforded 1-hydroxy-4-nitro-6-thia-10*b*-aza-2*a*-azoniaaceanthrylene hydroxide inner salt **VIII**. Treatment of compound **VII** with piperidine and piperazine in the presence of N,N-dimethylformamide gave substituted 1-hydroxy-2-piperidinoacetyl-4-nitro-6-thia-10*b*-aza-2*a*-azoniaaceanthrylene hydroxide inner salt **IX** and substituted 1-hydroxy-2-piperazinoacetyl-4-nitro-6-thia-10*b*-aza-2*a*-azoniaaceanthrylene hydroxide inner salt **X**, respectively. (Scheme).

Characterization data for all of the synthesized compounds have been tabulated in Table I. Compounds **V**, **VII**, **VIII**, **IX** and **X** were screened against *E. coli*, *S. aureus (bacteria)*, *A. flavus*, *A. niger*, *F. moniliformae and C. lunata* (fungi) (Table II).

## SPECTRAL STUDIES

### IR Spectra

In the IR spectra of compound **II**, a sharp band at 655-640 $cm^{-1}$ corresponding to C-S-C linkage was observed. Asymmetric and symmetric stretching vibra-



SCHEME 1

tions of the primary amino group appeared in the region 3450-3340 $cm^{-1}$. Compound **III** showed absorption bands at 1685-1680 $cm^{-1}$ and 3120-3080 $cm^{-1}$ due to carbonyl and secondary amino group, respectively, but primary amino group frequencies were absent. This confirmed the replacement of one hydrogen atom of $-NH_2$ by acetyl group. The absence of the >NH absorption in compound **IV** and presence of absorption at 1710-1690 $cm^{-1}$ due to the carbonyl group were in conformity with its structure. The presence of >NH absorption at 3300-3270 $cm^{-1}$ only in compounds **V** and **VI** indicated the free >NH at position-10.

TABLE I Characterization Data of the Title Compounds

| No. | $R^1$ | $R^2$ | $R^3$ | $R^4$ | Molecular formula | MP °C | Yield % | Elemental analysis Calcd. (fo | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | C | H |
| | H | Cl | $OCH_3$ | H | $C_{14}H_{10}ClN_3O_4S$ | 273–275 | 67 | 47.80 | 2.84 |
| | | | | | | | | (47.75) | (2.82) |
| | $CH_3$ | $CH_3$ | H | H | $C_{15}H_{13}N_3O_3S$ | 268–270 | 65 | 57.14 | 4.13 |
| | | | | | | | | (57.18) | (4.16) |
| | Cl | H | H | Cl | $C_{13}H_7Cl_2N_3O_3S$ | 289–291 | 63 | 43.82 | 1.96 |
| | | | | | | | | (43.80) | (1.94) |
| | H | H | $OC_6H_5$ | H | $C_{19}H_{13}N_3O_4S$ | >360. | 60 | 60.16 | 3.43 |
| | | | | | | | | (60.19) | (3.45) |
| | H | Cl | $CH_3$ | H | $C_{14}H_{10}ClN_3O_3S$ | 325–327 | 61 | 50.07 | 2.98 |
| | | | | | | | | (50.09) | (3.00) |
| | $OCH_3$ | H | H | Cl | $C_{14}H_{10}ClN_3O_4S$ | 311–312 | 63 | 47.80 | 2.84 |
| | | | | | | | | (47.83) | (2.86) |
| | H | Cl | $OCH_3$ | H | $C_{12}H_8ClN_3O_3S$ | 344–346 | 64 | 46.53 | 2.58 |
| | | | | | | | | (46.57) | (2.61) |
| | $CH_3$ | $CH_3$ | H | H | $C_{13}H_{11}N_3O_2S$ | >360 | 60 | 57.14 | 4.03 |
| | | | | | | | | (57.19) | (4.06) |
| | Cl | H | H | Cl | $C_{11}H_5Cl_2N_3O_2S$ | 339–341 | 59 | 42.04 | 1.59 |
| | | | | | | | | (42.00) | (1.54) |
| | H | H | $OC_6H_5$ | H | $C_{17}H_{11}N_3O_3S$ | 325–27 | 61 | 60.53 | 3.26 |
| | | | | | | | | (60.55) | (3.28) |
| | H | Cl | $CH_3$ | H | $C_{12}H_8ClN_3O_2S$ | 298–300 | 63 | 49.06 | 2.73 |
| | | | | | | | | (49.08) | (2.76) |
| | $OCH_3$ | H | H | Cl | $C_{12}H_8ClN_3O_3S$ | 262–265 | 63 | 46.53 | 2.58 |
| | | | | | | | | (46.55) | (2.61) |
| | H | Cl | $OCH_3$ | H | $C_{12}H_8ClN_3O_4S$ | 350–352 | 68 | 44.24 | 2.46 |
| | | | | | | | | (44.20) | (2.43) |
| | $CH_3$ | $CH_3$ | H | H | $C_{13}H_{11}N_3O_3S$ | >360 | 71 | 53.98 | 3.81 |
| | | | | | | | | (53.92) | (3.78) |

TABLE I (*con't*)

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| *Cl* | *H* | *H* | *Cl* | *$C_{11}H_5Cl_2N_3O_5S$* | *355–357* | *72* | *40.00* (40.06) | *1.52* (1.54) |
| H | H | $OC_6H_5$ | H | $C_{17}H_{11}N_3O_4S$ | 350–52 | 62 | 57.79 (57.81) | 3.12 (3.14) |
| H | Cl | $CH_3$ | H | $C_{12}H_8ClN_3O_3S$ | 320–22 | 61 | 46.53 (46.56) | 2.58 (2.60) |
| $OCH_3$ | H | H | Cl | $C_{12}H_8ClN_3O_4S$ | 345–47 | 63 | 44.24 (44.27) | 2.46 (2.48) |
| H | Cl | $OCH_3$ | H | $C_{16}H_9Cl_2N_3O_5S$ | 265–267 | 60 | 45.07 (45.01) | 2.11 (2.06) |
| $CH_3$ | $CH_3$ | H | H | $C_{17}H_{12}ClN_3O_4S$ | 256–258 | 68 | 52.37 (52.30) | 3.08 (3.02) |
| Cl | H | H | Cl | $C_{15}H_6Cl_3N_3O_4S$ | 215–219 | 65 | 41.81 (41.90) | 1.39 (1.43) |
| H | Cl | $OCH_3$ | H | $C_{14}H_8ClN_3O_4S$ | 223–225 | 58 | 48.07 (48.29) | 2.29 (2.28) |
| $CH_3$ | $CH_3$ | H | H | $C_{15}H_{11}N_3O_3S$ | 208–210 | 62 | 57.51 (57.80) | 3.51 (3.53) |
| Cl | H | H | Cl | $C_{13}H_5Cl_2N_3O_3S$ | 200–202 | 66 | 44.07 (44.26) | 1.41 (1.42) |
| H | Cl | $OCH_3$ | H | $C_{21}H_{19}ClN_4O_5S$ | >360 | 45 | 53.11 (52.86) | 4.00 (3.99) |
| $CH_3$ | $CH_3$ | H | H | $C_{22}H_{22}N_4O_4S$ | 318–320 | 50 | 60.27 (60.58) | 5.02 (5.04) |
| Cl | H | H | Cl | $C_{20}H_{16}Cl_2N_4O_4S$ | 344–346 | 54 | 50.10 (50.34) | 3.34 (3.33) |
| H | Cl | $OCH_3$ | H | $C_{20}H_{10}ClN_5O_5S$ | 300–303 | 35 | 50.47 (50.40) | 3.90 (3.88) |
| $CH_3$ | $CH_3$ | H | H | $C_{21}H_{21}N_5O_4S$ | 285 | 43 | 57.40 (57.46) | 4.78 (4.80) |
| Cl | H | H | Cl | $C_{19}H_{15}Cl_2N_5O_4S$ | 299–300 | 40 | 47.50 (47.28) | 3.13 (3.08) |

TABLE II Antimicrobial Activity of the Title Compounds

| | *Zone of inhibition in mm (Activity index)* | | | | | |
|---|---|---|---|---|---|---|
| | *S.a* | *E.c.* | *A.f.* | *A.n.* | *F.m.* | *C.l.* |
| Va | 10.0 | 11.2 | 10.5 | 10.5 | 11.0 | 10.8 |
| | (1.00) | (1.12) | (1.05) | (1.05) | (1.10) | (1.08) |
| Vb | 9.2 | 10.0 | 9.1 | 8.0 | 9.5 | 9.2 |
| | (0.92) | (1.00) | (0.91) | (0.80) | (0.95) | (0.92) |
| Vc | 8.7 | 9.5 | 10.0 | 6.7 | 8.2 | 8.2 |
| | (0.87) | (0.95) | (1.00) | (0.67) | (0.82) | (0.82) |
| Vd | 11.5 | 11.0 | 9.7 | 9.9 | 7.8 | 8.5 |
| | (1.04) | (1.00) | (1.14) | (1.16) | (0.91) | (1.00) |
| Ve | 9.9 | 9.5 | 8.9 | 8.5 | 7.2 | 6.9 |
| | (0.90) | (0.86) | (1.04) | (1.00) | (0.84) | (0.81) |
| Vf | 10.2 | 10.5 | 9.5 | 6.7 | 9.0 | 7.7 |
| | (0.91) | (0.95) | (1.05) | (0.78) | (1.05) | (0.90) |
| VIIa | 8.4 | 8.2 | 7.9 | 10.5 | 7.6 | 10.8 |
| | (0.84) | (0.82) | (0.87) | (0.95) | (0.76) | (0.96) |
| VIIb | 6.7 | 6.7 | 6.5 | 8.9 | 7.6 | 9.1 |
| | (0.67) | (0.67) | (0.71) | (0.81) | (0.76) | (0.81) |
| VIIc | 8.7 | 7.8 | 8.9 | 8.0 | 7.6 | 8.9 |
| | (0.87) | (0.78) | (0.98) | (0.73) | (0.76) | (0.79) |
| VIIIa | 8.5 | 7.9 | 9.5 | 11.0 | 8.9 | 11.0 |
| | (0.85) | (0.79) | (1.04) | (1.00) | (0.89) | (0.97) |
| VIIIb | 5.9 | 6.2 | 6.9 | 9.9 | 8.1 | 7.5 |
| | (0.59) | (0.62) | (0.76) | (0.90) | (0.81) | (0.66) |
| VIIIc | 6.8 | 6.9 | 7.8 | 10.2 | 7.9 | 8.9 |
| | (0.68) | (0.69) | (0.86) | (0.93) | (0.79) | (0.79) |
| IXa | 10.0 | 9.1 | 9.7 | 11.8 | 11.0 | 11.5 |
| | (1.00) | (0.91) | (1.07) | (1.07) | (1.10) | (1.02) |
| IXb | 7.7 | 8.9 | 9.0 | 11.2 | 9.5 | 10.5 |
| | (0.77) | (0.89) | (0.99) | (1.02) | (0.95) | (0.93) |
| IXc | 8.9 | 9.0 | 9.5 | 11.4 | 10.0 | 0.9 |
| | (0.89) | (0.90) | (1.05) | (1.04) | (1.00) | (0.96) |
| Xa | 10.9 | 11.5 | 10.1 | 12.5 | 12.0 | 12.4 |
| | (1.09) | (1.15) | (1.11) | (1.14) | (1.20) | (1.10) |
| Xb | 9.5 | 10.2 | 9.8 | 11.0 | 9.9 | 10.8 |
| | (0.95) | (1.02) | (1.08) | (1.00) | (0.99) | (0.96) |
| Xc | 10.0 | 10.5 | 10.9 | 11.5 | 8.9 | 11.2 |
| | (1.00) | (1.05) | (1.20) | (1.05) | (0.89) | (0.99) |

Activity index = Inhibition zone of the sample Inhibition zone of the standard

The IR spectra of compounds **VII**, **IX**, and **X** exhibited absorption due to an active methylene group at 2900-2820 $cm^{-1}$ and 1485-1435 $cm^{-1}$. Carbonyl frequencies of these mesoionic compounds were present at 1740-1700 $cm^{-1}$. These bands due to carbonyl and active methylene groups were not observed in the spectra of compound **VIII**.

### $^1$H NMR Spectra

The $^1$H NMR spectra of all the compounds showed a multiplet in the range δ 6.25–7.50 ppm due to phenyl protons. In compounds **II** and **III** the protons of the pyridine nucleus appeared at δ 9.10–9.38 ppm and in the remaining compounds in the range δ 7.74–8.10 ppm. These marked downfield shifts are due to the presence of nitro group(s). Spectra of compound **II** showed a broad singlet at δ 5.00–5.10 ppm due to $NH_2$ protons. The >NH proton in compounds **III**, **V** and **VI** exhibited a broad hump at δ 8.10–8.30 ppm. Singlets of methoxy and methyl protons appeared at δ 3.93–4.10 ppm and δ 2.08–2.20 ppm, respectively.

The -$CH_3$ protons of the -$NCOCH_3$ group of compounds **III** and **IV** appeared as sharp singlets at δ 3.50–3.53 ppm.

The active methylene group in compounds **VII**, **IX**, and **X** caused singlets in the spectra at δ 3.29–3.52 ppm. The piperidine protons of compound **IX** appeared as a complex multiplet at δ 3.71–4.01 ppm and piperazine protons (-$CH_2$-) of compounds **X** appeared as a broad singlet at δ 4.15–4.35 ppm.



## ANTIMICROBIAL ACTIVITY

The synthesized 10*H*-substituted-3-nitro-1-azaphenothiazines, mesoionic compounds and their derivatives were evaluated for their antimicrobial activities at a conc. of 100μg/disc in agar media using single disk method of A. W. Bauer *et al*[5]. Streptomycin and Mycostatin were used as the reference compounds in antibacterial and antifungal activities, respectively. All of the tested compounds were found to possess fair to good activities. The compounds with phenoxy and chloro-methoxy substituents were observed to exhibit better activities than others.

## EXPERIMENTAL

Melting points were determined in open capillary tubes and were uncorrected. IR (KBr; $\nu_{max}$ $cm^{-1}$) spectra were recorded on a Perkin-Elmer 577 grating spectrophotometer and $^1$H NMR spectra in DMSO-$d_6$ on a FX 90Q Jeol spectrophotometer at 90 MHz using TMS as the internal standard. The purity of the compounds was checked by TLC using silica gel 'G' as adsorbent.

**Synthesis of 2-Amino-4-chloro-5-methoxy-, 3,4-dimethyl-, 3,6-dichloro-, 5-phenoxy-, 4-chloro-5-methyl-, and 6-chloro-3-methoxy phenyl-2′-(3′, 5′-dinitro) pyridyl sulphide II**

A mixture of zinc mercaptide of a substituted 2-aminobenzenethiol (I; 0.005 mole), 2-chloro-3, 5-dinitropyridine (**II**; 0.01 mole), anhydrous sodium acetate (0.025 mole) and absolute ethanol (1.5 ml) was refluxed for 4 hr on a water bath. The solid obtained on cooling was collected by filtration, washed with water, dried and recrystallized from ethanol.

**Synthesis of 2-Acetylamino-4-chloro-5-methoxy-, 3,4-dimethyl-, 3,6-dichloro-, 5-phenoxy-, 4-chloro-5-methyl-, and 6-chloro-3-methoxy phenyl-2′-(3′,5′-dinitro) pyridyl sulphide III**

A solution of a 2-amino-substituted phenyl pyridyl sulfide (**II**; 0.005 mole) in pyridine (0.4 ml) and acetic anhydride (4.8 ml) was heated over a water bath for 2 hr. The solid separated on cooling and was filtered, washed with water, dried and recrystallized from isopropanol.



**Synthesis of 10-Acetyl-8-chloro-7-methoxy-, 8,9-dimethyl-, 6,9-dichloro-, 7-phenoxy-, 8-chloro-7-methyl-, and 6-chloro-9-methoxy-3-nitro-1-azaphenothiazine IV**

To a stirred, ethanolic solution of potassium hydroxide (0.28 g; 0.005 mole) and acetone (10 ml) was added under nitrogen atmosphere. This was followed by the addition of **III** (0.005 mole) and rapid reduction, by distillation, of the solvent to half of its original volume (5 ml). An equal volume of water (5 ml) was added to obtain a yellow solid product, which was collected by filtration, washed with water, dried and recrystallized from isopropanol.

**Synthesis of 10H-8-chloro-7-methoxy-, 8, 9-dimethyl-, 6, 9-dichloro-, 7-phenoxy-, 8-chloro-7-methyl-, and 6-chloro-9-methoxy-3-nitro-1-azaphenothiazine V**

To a refluxing solution of **III** (0.005 mole) in acetone (6.5 ml) was added potassium hydroxide (0.6 gm) in small portions and boiling was initiated and continued for 3 hr. Acetone was then distilled off and water (7.0 ml) was added to the residue. The product thus obtained was collected by filtration, washed well with water, and recrystallized from benzene.

### Synthesis of 10H-8-Chloro-7-methoxy-, 8,9-dimethyl-, 6,9-dichloro-, 7-phenoxy-, 8-chloro-7-methyl-, and 6-chloro-9-methoxy-3-nitro-1-azaphenothiazin-5-oxide VI

To a solution of a substituted-1-azaphenothiazine (**V**; 0.002 mole) in a hot mixture of dry ethanol (7.5 ml) and acetone (15 ml) was added hydrogen peroxide (0.002 mole or 0.2 ml of 30% w/v), and the reaction contents were then refluxed for 3 hr. The color of the solution darkened during refluxing. The solvent was then removed by distillation, and the residue was recrystallized from ethanol.

### Synthesis of 1-Hydroxy-2-chloroacetyl-4-nitro-6-thia-9-chloro-8-methoxy-, 9,10-dimethyl-, and 7,10-dichloro-10b-aza-2a-azoniaaceanthrylene Hydroxide VII

A stirred mixture of **V** (0.0025 mole), chloroacetic anhydride (0.0032 mole), and chloroacetic acid (0.008 mole) in dry dioxan (2.5 ml) was refluxed for 80 minutes. The hot solution was transferred into a beaker containing hot water (1 ml). The resultant precipitate was filtered and washed with warm ethanol (95%) until the washings were colorless.



### Synthesis of 1-Hydroxy-4-nitro-6-thia-9-chloro-8-methoxy-, 9, 10-dimethyl-, and 7,10-dichloro-10b-aza-2a-azoniaaceanthrylene Hydroxide VIII

Hydrolysis of **VII** (0.004 mole) was done via refluxing with a mixture of hydrochloric acid (1 ml) and gl acetic acid (3 ml) for 1.5 hr. Sodium hydroxide solution(aqueous) was added to this solution until it became alkaline. The resultant precipitate was filtered, dried, and recrystallized from ethanol.

### Synthesis of 1-Hydroxy-2-piperidinoacetyl-4-nitro-6-thia-9-chloro-8-methoxy-, 9,10-dimethyl-, and 7, 10-dichloro-10b-aza-2a-azoniaaceanthrylene Hydroxide IX

To a stirred solution of piperidine (0.022 mole) and DMF (20 ml) was added **VII** (0.007 mole). After completion of the addition, the reaction mixture was heated over a water bath for 1.5 hr. The reaction mixture was left overnight in a refrigerator. The solid that precipitated was collected by filtration. To the filtrate was added 1.5 ml of aq solution of $Na_2CO_3$ (5%) to facilitate precipitation of the

residual product left with the mother liquor. The total solid was washed well with water, dried, and recrystallized from isopropanol.

### Synthesis of 1-Hydroxy-2-piperazinoacetyl-4-nitro-7-thia-9-chloro-8-methoxy-, 9, 10-dimethyl-, and 7,10-dichloro-10b-aza-2a-azoniaaceanthrylene Hydroxide X

To a stirred solution of piperazine (0.022 mole) and DMF (20 ml) was added **VII** (0.007 mole). After completion of the addition, the reaction mixture was heated over a water bath for 1.5 hr. The reaction mixture was left overnight in a refrigerator. The solid that precipitated was collected by filtration. To the filtrate was added 1.5 ml of aq. solution of $Na_2CO_3$ (5%) to facilitate precipitation of the residual product was left with the mother liquor. The total solid was washed well with water, dried, and recrystallized from isopropanol. *



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