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SYNTHESIS OF S-OXIDES AND S,S-DIOXIDES OF SOME 4-NITRO- AND 4-AMINO-3-HYDROXY-10H-PHENOTHIAZINES AND -3H-PHENOTHIAZIN-3-ONES

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ABSTRACT

The S-oxides and S,S-dioxides of some 4-nitro- and 4-amino-3-hydroxy-10H-phenothiazines and –3H-phenothiazin-3-ones were obtained starting with 4-nitro-3H-phenothiazin-3-one (**2**) through selective reductions, followed of selective oxidations, O- and N-acetylations and condensation with benzaldehydes. The chemical structure of compounds was determined using chemical and spectral (^{1}H-NMR-, mass-, IR and UV-VIS spectroscopy) methods.

RESUMO

Os S-óxidos e S,S-dióxidos de algumas 4-nitro- e 4-amino-3-hidroxi-10H-fenotiazinas e 3H-fenótiazin-3-onas foram obtidos a partir de 4-nitro-3H-fenotiazin-3-ona (2) através de reduções seletivas seguidas por oxidações seletivas, O- e N-acetilações e condensações com benzaldeídos. A estrutura dos compostos foi determinada usando metodos químicos e espectroscópicos (^{1}H-RMN, espectrometria de massa e espectroscopia infravermelha e ultravioleta-visível).

KEYWORDS: **3H-phenothiazin-3-on-S-oxides and –S,S-dioxides, 10H-phenothiazin-S-oxides and –S,S-dioxides, O- and N-acylation, selective reduction, selective oxidation, ^{1}H-NMR spectra.**

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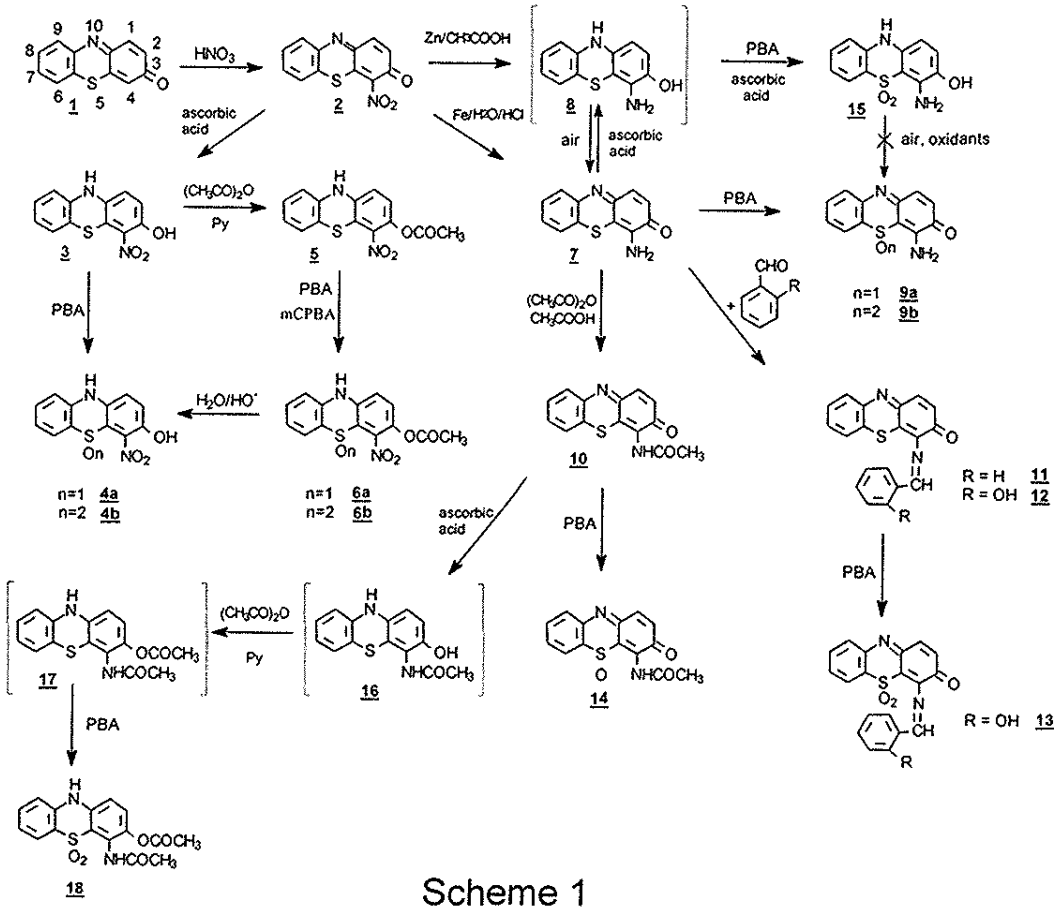
INTRODUCTION

The interest in phenothiazine derivatives covers a wide area, but the field with the most numerous applications is the pharmaceutical one due to the biological activity of the 10H-phenothiazine and N-substituted phenothiazines.[1-12] This type of compounds, substituted on the 10th position are used as antihelminthics,[2] antipsychotics,[3-5] insecticides,[6] antiseptics,[7] antimicrobials,[8,9] and anti-inflammatory agents[10-12] and are widely studied.

On the other hand, articles published on unsubstituted phenothiazines in the 10th position, are more scarce,[13-20] although these derivatives also have biological activity. Thus, some 3-hydroxy-10H-phenothiazin-S-oxides and S,S-dioxides inhibit lypoxygenase[21] and leucotriene biosynthesis[18,22] and were studied as metabolites of chlorpromazine with biological activity.[23] 3H-Phenothiazin-3-one (**1**) and its derivatives are cholinesterase[24] and leucotriene[18] inhibitors, and their analgesic[25] and antitumor[26] properties have been confirmed. However, 3H-phenothiazin-3-ones S-oxides and S,S-dioxides are less studied.[18]

In this context this paper deals with synthesis of some new 3-hydroxy-10H-phenothiazin- and 3H-phenothiazin-3-on-S-oxides and S,S-dioxides starting with 4-nitro-3H-phenothiazin-3-one (**2**). The compounds synthesized and the transformations studied are illustrated in Scheme 1.



Scheme 1

EXPERIMENTAL SECTION

The raw material that we used was 10H-phenothiazine which was oxidized[19,28] and then nitrated[15] to obtain 4-nitro-3H phenothiazin-3-one (**2**) [IR (KBr) 1315 (NO_{2sim}) 1520 (NO_{2asim}) 1665 (C=O) cm^{-1}; UV-VIS: 376 nm, 486 nm]. Reactions and the purity of the synthesised compounds were verified using thin layer chromatography. Elemental analyses correspond to the assigned structures. Mass spectrometric measurements were performed on a Matt 3.11 mass spectrometer. Varian Gemini 300 (300 MHz) apparatus was used to record ^{1}H-NMR spectra; proton chemical shift are relative to deuterium signal of DMSO-d_6 as internal standard. IR spectra were recorded on a Carl Zeiss Jena UR-10 spectrophotometer (KBr) and on a Specord IR 75 (Nujol). Electronic spectra were recorded in methanol on a Specord UV-VIS spectrophotometer. Melting points were taken on an Electrothermal apparatus and are uncorrected.

3-hydroxy-4-nitro-10H-phenothiazine (3). A mixture of **2** (1g, 3.9 mmol) and ascorbic acid (3g, 16.8 mmol) in isopropyl alcohol (200 mL) was stirred at room temperature for 2 hr; water (500 mL) was added to precipitate the crude **3**. Crystallisation from methanol afforded pure **3** as violet-greyish solid (0.9g, 89.3%, m.p.=176-8°C); IR (Nujol) 1300 (NO_{2sim}) 1460 (NO_{2asim}) 3370 (N-H) cm^{-1}; UV-VIS $\lambda(\varepsilon)$: 306 nm (5201), 465 nm (804).

3-hydroxy-4-nitro-10H-phenothiazin-5-oxide (4a). a). To a cooled solution (-10°C) of **3** (0,2g, 0.77 mmol) in chloroform (20 mL) was added under stirring PBA 6% (2 mL, 0.87 mmol); after 5 minutes the red insoluble solid was filtered and washed on filter (3x5 mL) with chloroform to afford **4a** (0.2g, 94%, m.p.=216-8°C); b). To a solution of **6a** (0.1g, 0.31 mmol) in acetone (50 mL) was added 20% aqueous NaOH (1 ml, 4 mmol), then the mixture was neutralised with 10% aqueous acetic acid causing precipitation of a red solid which, after filtering and washing with chloroform (3x5 mL), has the similar properties with **4a**; IR (Nujol) 985 cm^{-1} (S=O); UV-VIS $\lambda(\varepsilon)$: 364 nm (11326), 479 nm (6906).

3-acetoxy-4-nitro-10H-phenothiazine (5). A mixture of **3** (0.5g, 1.55 mmol), acetic anhydride (2 mL), pyridine (2 drops), and isopropyl alcohol (50 mL) was stirred at room temperature for 10 minutes, after which water was added (300 mL) causing precipitation of crude **5**. Crystallisation from methanol afforded pure **5** as brown fluffy crystals (0,5g, 84%, m.p.=164-6°C).

3-acetoxy-4-nitro-10H-phenothiazin-5-oxide (6a). To a solution of **5** (0.2g, 0.66 mmol) in chloroform (20 mL) was added dropwise PBA 6% (2 mL, 0.87 mmol) and stirred at room temperature for 10 minutes, when the yellow-orange suspension was filtered and the precipitate was washed with chloroform (3x10 mL) to afford **6a** as orange solid (0.2g, 95%, m.p.=226-8°C).

3-acetoxy-4-nitro-10H-phenothiazin-5,5-dioxide (6b). A mixture of **5** (0.3g, 0.99 mmol), mCPBA (2g, 11.6 mmol), methanol (30 mL) and methylene chloride (30 mL) was refluxed for 24 hr. After cooling down and evaporating to dryness, the residue was soaked with isopropyl alcohol (3x25 mL), then the resulted suspension was filtered to obtain the crude **6b**, which was soaked for 30 minutes with a mixture of benzene:acetone (4:1, 20 mL) to afford pure **6b**

(0.15g, 40.7%, m.p.=236-8°C) as beige fluffy crystals.

3-hydroxy-4-nitro-10H-phenothiazin-5,5-dioxide (4b). To a solution of **6b** (0.15g, 0.45 mmol) in acetone (20 mL) was added 20% aqueous NaOH solution (1 mL, 4 mmol), then the resulting solution was filtered and neutralised with 10% aqueous acetic acid, causing precipitation of crude **4b**, which was crystallised from methanol to afford pure **4b** (0.1g, 76,2%, m.p.=282-3°C) as light beige crystals.

4-amino-3H-phenothiazin-3-one (7). A mixture of **2** (1g, 3.9 mmol), NaCl (1g), 33% aqueous HCl (20 mL), water (200 mL) and Fe filings portionwise added was stirred vigorously at room temperature for 5 hr, then was added saturated aqueous $NaHCO_3$ solution to neutralise the mixture, when crude **7** precipitates; the purification of **7** was performed on a chromatographic column with Al_2O_3 III (500g) and toluene, the blue fraction was separated and vacuum distillated to afford pure **7** (0.6g, 67,89%, m.p.=185-6°C, lit.[17] 186-7°C) as acicular blue crystals; IR (KBr) 1650 (C=O), 3330-3415 (NH_2), (Nujol) 1565 (C=O) 3275-3370 (NH_2), lit.[17] (KBr) 1646 (C=O) 3324-3406 (NH_2) cm^{-1}; UV-VIS $\lambda(\varepsilon)$: 360 nm (9210) 616 nm (3296), lit.[17] (dioxane) 350 nm (12880) 587 nm (4860).

4-amino-3-oxo-3H-phenothiazin-5-oxide (9a). To a cooled solution (-10°C) of **7** (0.2g, 0.87 mmol) in chloroform (25 mL) was dropwise added PBA 6% (2.5 mL, 1.08 mmol) and stirred for 15 minutes, when the resulting suspension was filtered, and the precipitate washed with chloroform to afford **9a** (0.2g, 93.4%, m.p.=182-4 dec.) as orange solid; IR (Nujol) 965 (S=O) 1600 (C=O) 3240 (NH_2) cm^{-1}; UV-VIS $\lambda(\varepsilon)$: 402 nm (4157) 486 nm (6404).

4-amino-3-oxo-3H-phenothiazin-5,5-dioxide (9b). To a solution of **7** (0.3g, 1.3 mmol) in dioxane (50 mL) was added PBA 6% (7 mL, 3 mmol) and stirred at room temperature for 30 minutes, then was added chloroform (20 mL) and 2% aqueous borax solution (100 mL). The orange organic layer was washed with water, dried over Na_2SO_4 and evaporated to dryness. The crude **9b** was crystallised in methanol to afford **9b** as dark orange solid (0.15g, 43.8%, m.p.=302-5°C dec.).

4-(acetylamino)-3H-phenothiazin-3-one (10). A mixture of **7** (0.5g, 2.2 mmol), acetic anhydride (15 mL, 147 mmol), acetic acid (10 mL), and isopropyl alcohol (100 mL) was refluxed for two days; after cooling down and evaporating to one-half of the volume, the suspension was filtered and the precipitate was washed with methylene chloride (3x5 mL) to afford **10** as acicular cherry-coloured crystals (0.4g, 67.3%, m.p.=216-8°C).

4-(acetylamino)-3-oxo-3H-phenothiazin-5-oxide (14). To a solution of **10** (0.1g, 0.37 mmol) in methylene chloride (60 mL) was added PBA 6% (0.9 mL, 0.39 mmol). After one day the resulted suspension was filtered and the precipitate was washed with methylene chloride (3x5 mL) to afford **14** as orange solid (0.1g, 94.4%, m.p.=230-2°C).

4-(benzyliden-imino)-3H-phenothiazin-3-one (11). A mixture of **7** (0.2g, 0.87 mmol), benzaldehyde (5 mL), acetic acid (10 mL), and isopropyl alcohol (30 mL) was stirred at room temperature for 2 days; after evaporation to one-third of the volume, the resulted suspension was filtered and the precipitate

was crystallised from methanol to afford **11** (0.25g, 90.9%, m.p.=160-2°C) as violet fluffy crystals.

4-[(2'-hydroxy-benzyliden)-imino]-3H-phenothiazin-3-one (12). A mixture of **7** (0.2g, 0.87 mmol), salicylic aldehyde (5 mL), acetic acid (10 mL), and isopropyl alcohol (30 mL) was stirred at room temperature for 2 days; after evaporation to one-half of the volume, the resulted suspension was filtered and the precipitate was crystallised from methanol to afford **12** (0.2g, 69.2%, m.p.=204-6°C) as violet crystals; IR (KBr) 1625 (C=O) 3585 (O-H) cm^{-1}.

4-[(2'-hydroxy-benzyliden)-imino]-3-oxo-3H-phenothiazin-5,5-dioxide (13). To a mixture of **12** (0.2g, 0.6 mmol) and dioxane (20 mL) was added PBA 6% (10 mL, 4.16 mmol). After three days was added chloroform (20 mL) and 2% aqueous borax solution (100 mL), then the yellow organic layer was washed with water, dried over Na_2SO_4 and evaporated to dryness to obtain crude **13**, which was soaked with benzene, and then the suspension is filtered to afford pure **13** (0.1g, 45,8%, m.p.=295-7°C); IR (KBr) 1130 (SO_{2sim}) 1330 (SO_{2asim}) 1653 (C=O) 3450 (O-H) cm^{-1}.

4-amino-3-hydroxy-10H-phenothiazine (8). "In situ" obtaining. To a solution of **7** (0.2g, 0.87 mmol) in isopropyl alcohol (50 mL) was added ascorbic acid (1g, 5.6 mmol) and stirred at room temperature for 15 minutes to afford the light yellow solution of **8**.

4-amino-3-hydroxy-10H-phenothiazin-5,5-dioxide (15). To the solution of **8** was added under vigorously stirring and dropwise PBA 6% (8 mL, 3.32 mmol); after 10 minutes was added chloroform (20 mL) and 2% aqueous borax solution (100 mL); then the yellow organic layer was washed with water, dried over Na_2SO_4 and evaporated to dryness. The residue was soaked with benzene, and the resulting suspension was filtered and the filtrate was evaporated to dryness to afford **15** (0.1g, 45.4%, m.p.=175-6°C dec.) as light brown solid.

4-(acetylamino)-3-hydroxy-10H-phenothiazine (16). "In situ" obtaining. To a solution of **10** (0.2g, 0.74 mmol) in dioxane (50 mL) was added ascorbic acid (1g, 5.6 mmol) and stirred at room temperature for 30 minutes to afford the light red solution of **16**.

4-(acetylamino)-3-acetoxy-10H-phenothiazine (17). "In situ" obtaining. To the solution of **16** was added acetic anhydride (5 mL, 49 mmol) and pyridine (1 mL) and the mixture was stirred at room temperature for 1 hr to afford the red solution of **17**.

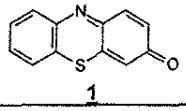
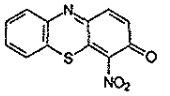
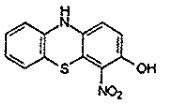
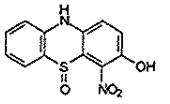
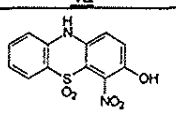
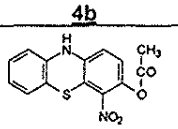
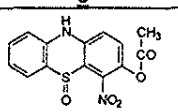
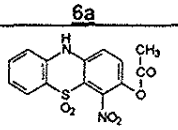
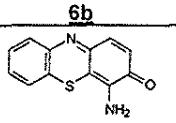
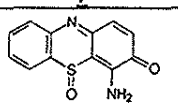
4-(acetylamino)-3-acetoxy-10H-phenothiazin-5,5-dioxide (18). To the solution of **17** was added PBA 6% (10 mL, 4.16 mmol) and stirred at room temperature for 1 hr, then was added chloroform (20 mL) and 2% aqueous borax solution (100 mL); then the organic layer was washed with water, dried over Na_2SO_4 and evaporated to dryness. The residue was soaked with benzene, the resulting suspension was filtered to afford **18** (0.1g, 35%, m.p.=252-4°C) as light red solid.

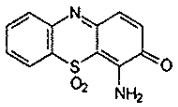
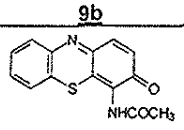
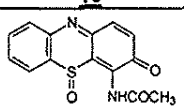
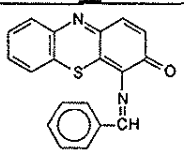
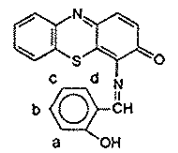
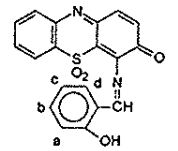
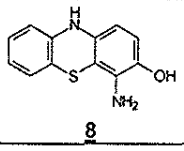
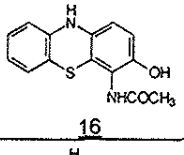
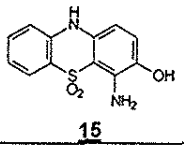
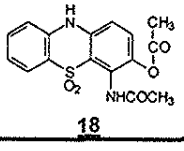
RESULTS AND DISCUSSION

The ^{1}H-NMR parameter of the synthesised compounds are presented in

Table 1. Other parameters (m.p., m/e, ν, λ_{max}) are indicated in the Experimental section and the discussion context.

Table 1. ^{1}H-NMR Parameters of Synthesised Compounds [chemical shift (δ, ppm), coupling constant (J, Hz) and multiplicity*]

No.	COMPOUND	PHENOTHIAZINIC PROTONS							OTHER PROTONS
		H^1	H^2	H^6	H^7	H^8	H^9	H^{10}	
1	2	3	4	5	6	7	8	9	10
1.	 1	7.67 10.20 d	6.90 10.20 d	7.56-7.58 - m	7.65-7.68 - m	7.56-7.58 - m	7.88 - m	-	H^4: 6.86, s
2.	 2	7.89-7.99 - m	7.14 10.00 d	7.89-7.99 - m	8.16-8.25 - m	7.89-7.99 - m	8.17 7.22; 1.68 dd	-	-
3.	 3	6.75-7.10 - m						8.73 - s	O-H: 10.59, s
4.	 4a	7.55 9.12 d	7.42 9.07 d	7.92 7.63 d	7.20 7.44 t	7.61 7.31 t	7.41 8.12 d	11.23 - s	
5.	 4b	7.48 8.82 d	7.43 8.82 d	7.85 7.64 d	7.26 7.64 t	7.67 7.64 t	7.36 7.64 d	11.08 - s	
6.	 5	7.10 8.80 d	6.96 8.80 d	7.02 7.63 d	6.86 7.45 t	7.10 7.63 t	6.77 7.63 d	9.20 - s	CH_3: 2.24, s
7.	 6a	7.74 - s	7.74 - s	7.99 7.68 d	7.30 7.42 t	7.71 7.54 d	7.50 8.18 m	11.64 - s	CH_3: 2.31, s
8.	 6b	7.65 9.12 d	7.80 9.33 d	7.91 8.01 d	7.35 7.54 t	7.75 7.65 t	7.44 8.37 d	11.53 - s	CH_3: 2.30, s
9.	 7	7.41 9.83 d	6.89 9.83 d	7.39-7.43 - m	7.52 5.0 t	7.65 5.0 t	7.39-7.43 - m	-	H-N: 5.70, br s
10.	 9a	7.40 10.06 d	6.74 10.06 d	7.87 8.71 d	7.50-7.60 - m	7.71 - m	7.50-7.60 - m	-	NH_2: 7.71, m

1	2	3	4	5	6	7	8	9	10
11.	 **9b**	7.34 10.08 d	6.76 10.08 d	8.01 7.47 d	7.62 7.17 t	7.78 6.90 t	7.70 7.47 d	-	H-N: 8.15, s
12.	 **10**	7.70 9.89 d	7.06 9.65 d	7.58- 7.63 - m	7.97 2.93;4.9 2 t	7.87 7.8 t	7.58- 7.63 - m	-	CH_3: 2.06, s N-H: 9.78, s
13.	 **14**	7.30 10.29 d	6.77 10.38 d	7.99 7.20 d	7.53 - m	7.76 - m	7.53 - m	-	CH_3: 2.13, s H-N: 5.76, s
14.	 **11**	7.71 9.63 d	7.07 9.81 d	7.94 7.41 d	7.86- 7.89 - m	7.49-7.52 - m	8.01 6.75 d	-	N=C-H:9.13, s C_6H_5: 7.59, m
15.	 **12**	7.75 9.45 d	7.09 9.87 d	7.80 7.83 d	7.98 - m	7.41 7.41 t	7.91 4.47 d	-	N=C-H:9.41, s O-H: 12.02, s H^a, H^c: 7.01-7.04, m H^b, H^d: 7.62-7.64, m
16.	 **13**	8.17 8.81 d	7.41 8.81 d	8.06 7.76 d	7.58 7.76 t	7.70 7.76 t	7.79 7.76 d	-	C-H:11.22, s O-H: 11.34, s H^a: 7.08, d, 7.34 H^b: 7.31, t, 7.34 H^c: 7.13, t, 7.34 H^d: 7.38, d, 7.34
17.	 **8**	5.92 8.01 d	6.37 8.19 d	6.94 8.00 m	6.64- 6.72 - m	6.95 8.17 t	6.64- 6.72 - m	8.07 - s	O-H: 8,78, s
18.	 **16**	6.46 8.19 d	6.52 8.19 d	6.88 7.62 d	6.68 7.14 t	6.94 7.17 t	6.63 7.53 d	8.2 - s	H-O: 8,86, s 4-CO-N-H: 9,17, s
19.	 **15**	6.37 9.00 d	6.94 9.00 d	7.80 7.50 d	7.10 7.50 t	7.55 7.50 t	7.20 7.50 d	10.32 - s	H-O: 9.41, s H-N: 6.64, s H-N: 6.83, s
20.	 **18**	7.26-7.31 - m	7.48 9.08; 2.49 dd	7.87 8.16; 1.32 dt	7.26- 7.31 - m	7.64 7.8; 1.36 tt	7.22 7.95; 2.19 dd	10.98 - s	CH_3^3: 2.20 CH_3^4: 2.08 4-CO-N-H: 9.45, s

*multiplicity: s: singlet; d: doublet; t: triplet; dd: doublet of doublets; dt: doublet of triplets; tt: triplet of triplets; m: complex multiplet. CD_3SOCD_3 was used as solvent with an exception: **2** was solved in $CDCl_3$.

The starting compound 4-nitro-3H-phenothiazin-3-one (**2**) was synthesised from 3H-phenothiazin-3-one (**1**).[15] Nitration of **1** in the 4th position is proved by the absence of the corresponding signal of the 4th position hydrogen atom in the ^{1}H-NMR spectrum of the 3H-phenothiazin-3-one (**1**) nitration product **2**, while the complexity of the other signals excludes the fact that the nitration occurred in the 7th position claimed before.[27] On the other hand, all of the ^{1}H-NMR spectra of the synthesised compounds from the nitration product **2** confirm the occupation of the 4th position (there does not appear any singlet signal) and the fact that the carbon atom C^7 is linked to an hydrogen atom (the signals corresponding to H^7 and H^8 appear mostly as triplet and to H^6 and H^9 as doublet, respectively) (Figure 1).

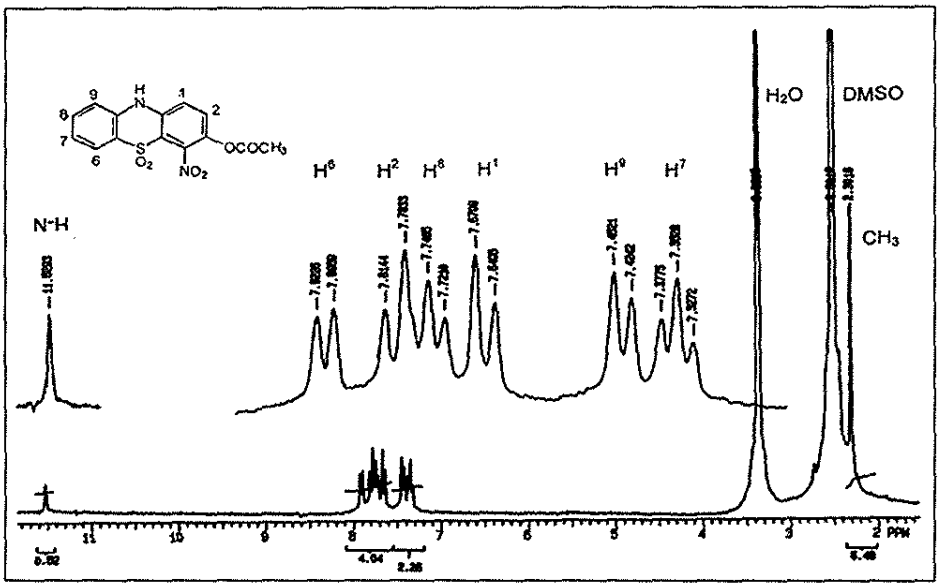


Figure 1. ^{1}H-NMR Spectrum of 3-Acetoxy-4-nitro-10H-phenothiazin-5,5-dioxide (**6b**) (DMSO-d_6)

Because of the presence of the p-quinon-iminic system in the 3H-phenothiazin-3-ones which is easy to reduce,[13,14,17,18] we have tried the selective reduction its in the case of 4-nitro-3H-phenothiazin-3-one (**2**). The reduction of **2** with ascorbic acid led to 3-hydroxy-4-nitro-10H-phenothiazine (**3**); the presence of the p-hydroquinon-aminic system in **3** is proved by the ^{1}H-NMR spectrum where two singlet signals appears (8,37 ppm and 10,59 ppm) corresponding to the 10th position and hydroxyl group hydrogens and a general upfield shift of the hydrogens, and of the mass spectrum [m/e=260 ($M^{+\cdot}$)], respectively.

From the literature [13,14] is well known that perbenzoic acid (PBA) undergoes the selective oxidation of the sulphur atom, because this oxidation agent has an affinity for nonparticipating electrons of the sulphur atom.

Oxidising **3** with PBA in small excess we have obtained 3-hydroxy-4-nitro-10H-phenothiazin-5-oxide (**4a**). This selective oxidation is proved by the ^{1}H-NMR spectrum (δ_{N-H}=11,23 ppm), mass spectrum [m/e=276 ($M^{+\cdot}$)] and the IR one ($\nu_{S=O}$=985 cm^{-1}). The attempt to obtain directly the corresponding S,S-

dioxide **4b** through the oxidation of **3** with PBA in large excess led to a mixture of **4b** and **2**, because the excess of PBA induced the oxidation of the p-hydroquinon-aminic system, and the conversion was low due to the small solubility of the intermediate S-oxide (**4a**).

In order to avoid the oxidation of the p-hydroquinon-aminic system, the **3** was O-acetylated to obtain 3-acetoxy-4-nitro-10H-phenothiazine (**5**) [δ_{N-H}=9,20 ppm, δCH_3=2,24 ppm, m/e=302 ($M^{+\cdot}$)]. The oxidation of **5** with PBA even in great excess led only to the corresponding S-oxide [δ_{N-H}=11,64 ppm, m/e=318 ($M^{+\cdot}$)], (Figure 2).

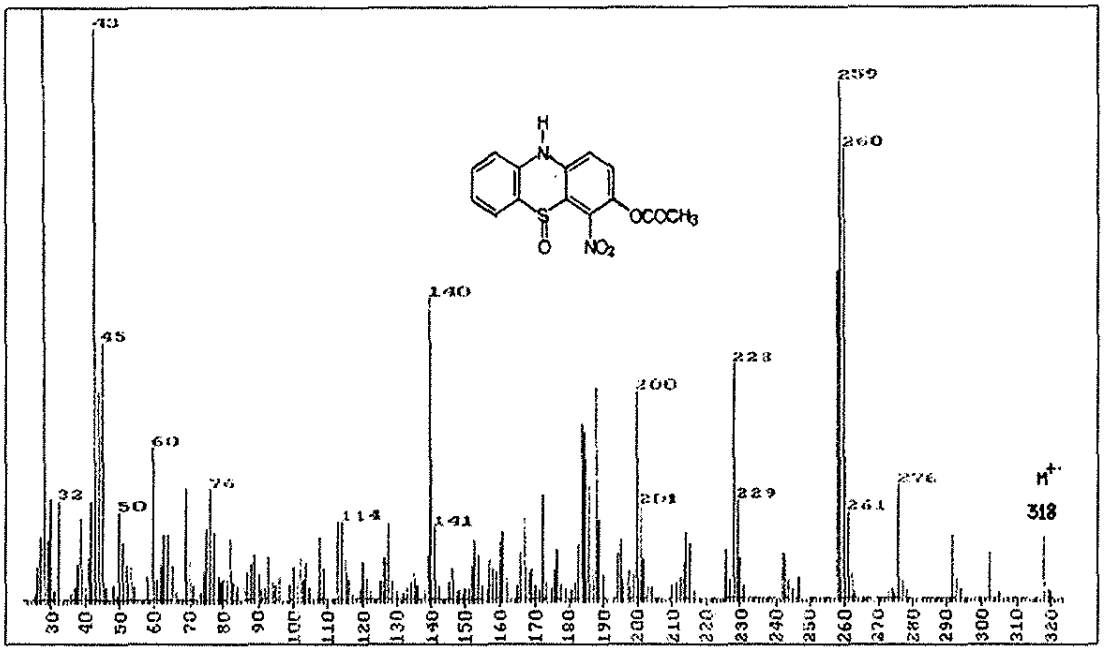


Figure 1. ^{1}H-NMR Spectrum of 3-Acetoxy-4-nitro-10H-phenothiazin-5-oxide (**6a**) (DMSO-d_6)

The corresponding S,S-dioxide **6b** was obtained using m-chloro-peroxybenzoic acid (mCPBA) in harder conditions (refluxed for 24 hours). The S,S-dioxide **4b** was easily obtained through basic hydrolysis of **6b** [δ_{N-H}=11,08 ppm, m/e=292 ($M^{+\cdot}$)]. By hydrolysing the **6a** we obtained a red coloured compound which presents the same characteristics as the S-oxide **4a**. In the ^{1}H-NMR spectra of **4a** and **4b** the signals of the hydroxy group do not appear because the signal is expanded and flattened due to the proton exchange with water from the solvent (DMSO-d_6).

The selective reduction of nitro group from 4-nitro-3H-phenothiazin-3-one (**2**) was performed with Fe/H_2O/HCl to obtain 4-amino-3H phenothiazin-3-one (**7**). A small amount of 4-amino-3-hydroxy-10H-phenothiazine (**8**) was also obtained as shown by thin layer chromatography (TLC), which was rapidly oxidised to **7** by air. We have to mention that this reduction was previously done[17] with Zn/CH_3COOH, but with lower yield. Our reduction product (**7**) has the same properties (m.p., IR, UV-VIS data) as those from literature. The ^{1}H-NMR (absence of 4th, 10th positions and O-H hydrogens corresponding signals) and mass [m/e=228 ($M^{+\cdot}$)] spectra confirm the assigned structure.

In order to prove in a chemical way the presence of the amino group, **7** was acetylated and condensed with carbonyls. Another reason for these reactions was to protect the amine group against oxidation.

The oxidation of **7** with a small excess of PBA led to 4-amino-3-oxo-3H phenothiazin-5-oxide (**9a**) [$\nu_{S=O}$=965 cm^{-1}, m/e=244 ($M^{+\cdot}$)]. Using a greater excess of PBA we obtained a mixture of oxidation products, out of which we could isolate the corresponding sulphone 4-amino-3-oxo-3H phenothiazin-5,5-dioxide (**9b**) [m/e=260 ($M^{+\cdot}$)].

The reactivity of amino group as nucleophile is decreased because the nonparticipating electrons of nitrogen interact with the phenothiazine Π electron system of **7**, and because of that, N-acetylation needs drastic conditions (excess of reagents, acid environment). For condensation we have chosen carbonyls with increased reactivity (benzaldehyde, salicylic aldehyde). Thus, 4-acetylamino-3H-phenothiazin-3-one (**10**), 4-benzylidenimino-3H-phenothiazin-3-one (**11**), and 4-(2'-hydroxy-benzyliden)imino-3H-phenothiazin-3-one (**12**), were obtained and were afterwards oxidised. The oxidation of these compounds occurred slowly because of sterical impediments brought by sizeable groups linked in the 4th position, which required the use a large excess of PBA (350-500%). This large excess led to complex mixtures of oxidation compounds, out of which we could isolate only 4-(2'-hydroxy-benzyliden)imino-3-oxo-3H-phenothiazin-5,5-dioxide (**13**) [νSO_{2sim}=1130 cm^{-1}, νSO_{2asim}=1330 cm^{-1}, m/e=364 ($M^{+\cdot}$)]. Surprisingly, using just a stoichiometric amount of PBA we obtained the corresponding S-oxide of **10**, 4-acetylamino-3-oxo-3H-phenothiazin-5-oxide (**14**). The hydrolysis of **13** and **14** performed in order to obtain **9b** and **9a**, respectively, was unsuccessful.

The reduction of p-quinon-iminic system from **7** with ascorbic acid occurs rapidly to obtain "in situ" 4-amino-3-hydroxy-10H-phenothiazine (**8**). All attempts to isolate **8** led to a mixture in which **7** was prevalent, because of the oxidation tendency of p-hydroquinon-aminic system, tendency that is increased by the amino group. The oxidation of **8** obtained "in situ", with PBA, led to a yellow-brown compound which has two singlet signals (9,41 ppm and 10,32 ppm) corresponding to a p-hydroquinon-aminic system (O-H and N-H, respectively) in the ^{1}H-NMR spectrum, proving the formation of 4-amino-3-hydroxy-10H-phenothiazin-5,5-dioxide (**15**). The existence of withdrawing sulphone group in **15** induced a relative stability of p-hydroquinon-aminic system. On the other hand, this sulphone group, which is *ortho* to the amino group, led to a destabilisation of the molecule, so **15** was unstable in solid state in the presence of air.

In order to improve the synthesis of **15** we have protected the p-hydroquinon-aminic system and the amino group by acylation. Thus, we have O-acylated "in situ" 4-acetylamino-3-hydroxy-10H-phenothiazine (**16**), which was obtained through reduction of **10** with ascorbic acid. The intermediate 4-acetylamino-3-acetoxy-10H-phenothiazine (**17**) was oxidised "in situ" to the corresponding S,S-dioxide **18**, which ^{1}H-NMR spectrum has the signals corresponding to the 10th position and acetylaminic hydrogens (10,97 ppm and 9,45 ppm, respectively) as well as the signals of the two methyl groups of O- and N-acetyls (2,20 ppm and 2,08 ppm, respectively). The basic or the acid

hydrolysis of **18** led to complex mixtures, out of which we could not isolate the expected sulphone **15**.

CONCLUSIONS

In this paper we report the obtainment of fifteen new 10H-phenothiazine and 3H-phenothiazin-3-one compounds. Among these ten are S-oxides and S,S-dioxides, respectively. We did not succeeded to isolate the S-oxide or S,S-dioxide corresponding to 4-nitro-3H phenothiazin-3-one (**2**), unlike 4-amino-3H-phenothiazin-3-one (**7**) and its 4-amino group derivatives (**10**-**12**). This difference of reactivity seems to have an electronic reason (the strong positivation of the sulphur atom in **2**). However, 4-nitro-10H-phenothiazine derivatives (**3**, **5**) gave S-oxides and S,S-dioxides with peracids.

We also noticed the stability of S-oxides and S,S-dioxides (**9a**, **9b**, **13**, **14**) toward nucleophilic addition in 4th and 10th positions, addition that occurred at the unsubstituted in 4th position analogs.[18] This differentiation allowed us to directly synthesise S-oxides and S,S-dioxides **9a**, **9b**, **13**, **14**.

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