NEW SCHIFF BASES DERIVED FROM 3-FORMYL-10-ALKYL-PHENOTHIAZINE I. NMR AND UV-VIS STRUCTURAL ASSIGNMENTS.

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Abstract: A series of new Schiff bases prepared by the condensation of 3-formyl-10-alkyl-phenothiazine with aromatic and heteroaromatic (di)-amines under conventional heating and microwave activation conditions were analysed. The structures of the new compounds were assigned by 400 MHz 2D-NMR experiments. Photochemical *E-Z* isomerisation and decomposition has been observed. The extended □ electron systems were characterized by an absorption band situated at 520 nm in the UV-Vis absorption spectra.

Introduction

A series of Schiff bases derived from 3-formyl-10-methyl-phenothiazine, prepared by condensation with aliphatic or aromatic diamines, were previously reported [1,2].

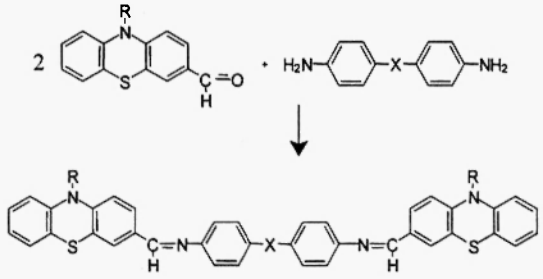
The linear structure and the extended □ electron system in *N*-(10-alkylphenothiazine-3-methylidene)aromatic amine conjugation could develop interesting electrical or biological properties, a fact that encouraged us to synthesize new representative compounds. The paper presents the first in a series of structural assignments for the new compounds, namely high resolution 2D-NMR experiments and UV-Vis absorption spectra.

Results and discussion

A series of Schiff bases derived from 3-formyl-10-alkyl-phenothiazine prepared by the condensation of 3-formyl-10-ethyl-phenothiazine [3], or 3-formyl-10-methyl-phenothiazine [3] with aromatic diamines (scheme 1) and 5-amino-substituted pyrazoles [4] (scheme 2) were analysed.

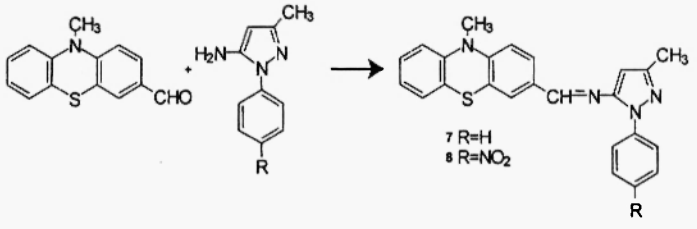
The condensation reactions were carried out in polar solvent (alcohol), by refluxing several hours the phenothiazine derivative with the diamine in a 2:1 molecular ratio. The reaction progress was followed by TLC. The products were purified by column chromatography. Thus, *N,N'*-bis(10-ethyl-phenothiazine-3-methylidene)*p,p'*-diamino-diphenylmethane **1** was obtained in 80% yield as á yellow crystalline precipitate, after 2 hours in refluxing

methanol; *N,N'*-bis(10-ethyl-phenothiazine-3-methylidene)*p,p'*-diamino-1,2-diphenylethane **2** was obtained in 70 % yield after 5 hours in refluxing methanol, and *N,N'*-bis(10-ethyl-phenothiazine-3-methylidene)*p,p'*-diaminodiphenylether **3**, appears as a yellow precipitate after 6 hours in refluxing isopropanol. A slight excess of 3-formyl-10-ethyl-phenothiazine usually improves the yield in *bis* Schiff base. The same procedure was applied to the syntheses of 3-formyl-10-methyl-phenothiazine Schiff base derivatives: *N,N'*-bis(10-methyl-phenothiazine-3-methylidene)*p,p'*-diaminodiphenylmethane **4**, *N,N'*-bis(10-methyl-phenothiazine-3-methylidene)*p,p'*-diamino-1,2-diphenylethane **5**, *N,N'*-bis(10-methyl-phenothiazine-3-methylidene)*p,p'*-diaminodiphenylether **6**.



Scheme 1

Condensation products from 3-formyl-10-methyl-phenothiazine with 5-amino-pyrazolyl derivatives: *N*-(10-methyl-phenothiazine-3-methylidene)5-amino-3-methyl-1-phenylpyrazol **7**, and *N*-(10-methyl-phenothiazine-3-methylidene) 5-amino-3-methyl-1-(*p*-nitrophenyl)pyrazol **8**, were obtained after 10 hours in refluxing methanol.



Scheme 2

Microwave activation of these condensation reactions determined shorter reaction times for obtaining the same products (table 2). The reactions were performed in a modified domestic microwave oven, under dry conditions, in quartz open vessel. The tested dry supports were bentonite, aluminium oxide and silica gel; the last one was selected as it gave the best yields in Schiff *bis* bases formation. Thus, a chloroform solution of reagents (2 mol carbonyl compound and 1 mol amine) was mixed with silica gel, the solvent evaporated and the dry reaction mixture was heated in the microwave oven for 1-2 minutes. The reaction products were extracted with dichloromethane, the solvent evaporated and the crude product purified.

Structural assignments of these new compounds were based on the 400 MHz ^{1}H-NMR spectroscopic data and ^{13}C-NMR spectra. The assignments of overlaping ^{1}H-NMR and ^{13}C-NMR signals were performed using 2D-NMR H-C correlation spectra. Quaternary carbon atoms were assigned using 2D H-C inverse long range correlation spectra.

^{1}H-NMR spectra data of compounds **1-3,** in C_6H_6-d_6 and DMSO-d_6 solvent were compared. The azomethyne group, as a solvatation center of the Schiff base molecule affects the chemical shift of the neighboring protons; thus, the H_{3a} proton (figure 1) appears in compound **3** more shielded in C_6H_6-d_6 (δ_{H3a}= 8.08 ppm, probably due to donor acceptor π interactions) and more deshielded in DMSO-d_6 solvent (δ_{H3a}= 8.51 ppm, probably due to hydrogen bonding). The same solvent effect can be observed upon neighboring aromatic protons H_c (δ_{Hc}= 7.18 ppm in C_6H_6-d_6 and δ_{Hc}= 7.31 ppm in DMSO-d_6) and H_2 (δ_{H2}= 7.71 ppm in C_6H_6-d_6 and δ_{Hc}= 7.73 ppm in DMSO-d_6). The solvatation around the phenothiazine part of the Schiff base molecule by benzene, determines smaller chemical shift values for adjacent protons, as compared to the values recorded in chloroform or DMSO, and a shielding effect upon H_8 (δ_{H8}= 6.87 ppm) as compared to H_6 (δ_{H6}= 6.99 ppm), the latter appearing more shielded in polar solvents.

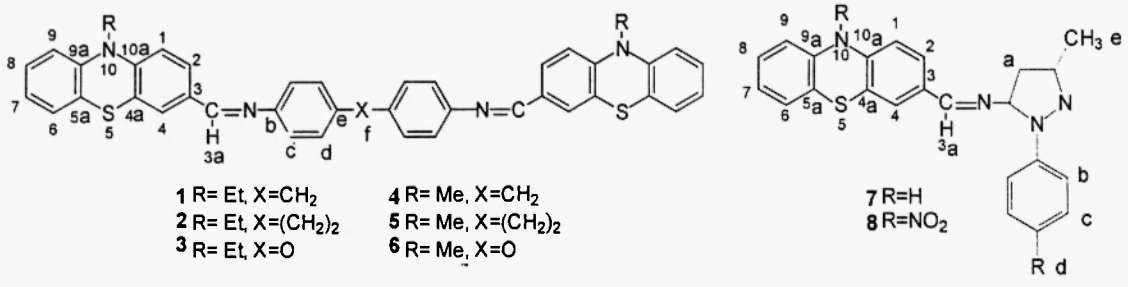


Fig. 1 The atoms labelings in structural formulas of compounds **1-8**

The effect of visible light upon DMSO-d_6 solutions of **3,** leads to a new compound characterized in ^{1}H-NMR spectrum by an additional singlet peak situated at δ= 8.27 ppm, assigned to the azomethyne group proton of a *Z* isomer of compound **3,** in which the deshielding anisotrope effect of phenyl group is suppressed; ^{1}H-NMR observed isomeres *E*:*Z* ratio was 1:0.06.

Photochemical reaction of Schiff bases **4,** 6 and 7 performed in chloroform 1% solutions, upon 15 minutes irradiation, using the 254 nm wave length emited by a 7W power UV lamp, determined the decomposition of the Schiff base structure to the corresponding formyl derivative. The reaction mixtures obtained were analysed by quantitative ^{1}H-NMR; the ratio between the corresponding decomposition formyl derivative and the *E* Schiff base was 0.15:1 for compound **4,** 0.03:1 for compound 6 and 0.21:1 for compound **7.**

400 MHz ^{1}H-NMR and 2D correlation spectra were used for the structural investigations of substituted pyrazolo derivatives 7 and **8.** The 2D-NMR COSY 45 spectrum of compound **8,** presents long range coupling interactions (^{4}J) between the azomethyne group proton H_{3a} (δ= 8.48 ppm) and the phenothiazine protons $H_{2,4}$ (δ= 7.59 ppm), and a ^{5}J coupling with pyrazolo group proton H_a (δ= 6.15 ppm). These NMR structural assignments are in good agreement with the spatial structure of an "*E* folded " diastereoisomer.

UV-Vis spectra of compounds **1, 2, 3,** 7 and **8** were registered in chloroform solution and typical absorbances are presented in table 1

All analysed Schiff bases, presented a pale yellow colour due to the absorption band situated near 400 nm.

An additional low extinction absorption band situated at 520 nm is characteristic to all compounds containing the chromofore system *N*-(10-alkyl-phenothiazine-3methylidene)benzenamine, described by both neutral and intramolecular charge transfer structures. This absorption band is missing in compounds **7**, **8** (where phenyl group has been replaced by pyrazolyl nucleus), and also in similar compounds where phenothiazine nucleus was replaced by other aromatic structures (*e.g.* phenylene).

Table 1. Typical absorbances in the UV-Vis spectra of compounds **1, 2, 3, 7** and **8** (in chloroform)

Compound	λ [nm]
1	250, 285, 390, **520**
2	248,280,340, 380, **520**
3	250, 290, 390, **520**
7	250,295,410
8	320,420

An absorption band situated at 515 nm was previously assigned to the phenothiazine cation-radical [5]. The absorption band situated at 520 nm in the recorded UV-VIS spectra of Schiff bases, raise in intensity on dilution or addition of small amounts of HCl, a fact that might be explained by the existence of a phenothiazine cation-radical unit into the intramolecular charge transfer structure, which appears to be more stable in polar solvent.

Experimental

3-Formyl-N-methylphenotiazine[3]

30mL DMF were treated dropwise with 10mL phosphorous oxychloride (under external cooling with ice), then with 20g of 10-methyl-phenotiazine. The mixture was heated for 2 hours on a steam bath, then poured on 500g of ice. The pH was then adjusted to approx. 6 with an aqueous solution of sodium acetate. The resinous product separated was extracted at room temperature with four portions of 200ml toluene each. The toluenic extract was dried on anhydrous sodium sulphate, then concentrated by distillation under reduced pressure on a steam bath to 200mL, then chromatographed on a column with Silica gel 60. The solvent was evaporated to dryness under reduced pressure on a steam bath and the residue was recrystallized from ethanol yielding 12g.

General procedure for Schiff bases preparation

a. 3-Formyl-10-alkyl-phenothiazine (2 mmol) and aromatic diamine (1 mmol) were refluxed in alcohol solutions several hours (table 2). The reaction progress was monitored by TLC. After solvent evaporation, the product was purified by column chromatography (silica gel 60 stationary phase and toluene eluent); after solvent distillation, yellow powder products were obtained. Melting points and characteristic yields are presented in table 2.

b. 3-Formyl-10-alkyl-phenothiazine (2 mmol) and aromatic diamine (1 mmol) were solved in 15 ml chloroform; 2 g of silica gel 60 were added and the solution evaporated to dryness. The reaction mixture was heated in a quartz sample tube for 1-2 minutes (table 2) at 650W power. Products were extracted with dichlorometane, the solvent evaporated and the crude product was purified by recrystallisation. Yields are presented in table 2.

Table 2. Chemical data for compounds **1-8**

Comp.	Solvent Classical	Reaction Time		Yield [%]		M.p.[°C]
		Classical[h]	Microwave[min.]	Classical	Microwave	
1	MeOH	2		85		149
2	MeOH	5		85		227
3	i-PrOH	6		70		135
4	EtOH	6	1.5	85	44	215
5	EtOH	6	1.5	90	65	264
6	EtOH	4	1.5	85	63	229
7	MeOH	6	1.5	70	56	151
8	MeOH	10	1.5	85	65	188

NMR and SM data for compounds 1-8 (400 MHz, $CDCl_3$)

N,N'-bis(10-ethyl-phenothiazine-3-methylidene)*p,p'*-diamino-diphenylmethane **1**.
^{1}H-RMN δ(ppm) 4.0(s, 2H), 7.20(d, 4H), 7.13(d, 4H), 7.65(d, 2H), 7.61(dd, 2H), 7.14(t, 2H), 7.10(dd, 2H), 6.92(t, 2H), 6.87(d, 2H), 6.88(d, 2H), 1.44(t, 6H), 3.96(q, 4H).
^{13}C-RMN δ(ppm) 12.9, 40.9, 158.3, 115.2, 114.6, 121.0, 129.6, 123.0, 124.0, 122.9, 127.4, 127.3, 127.1, 128.5, 130.7, 144.2, 147.8, 150.2, 138.7, 42.1.
SM (m/e) 672

N,N'-bis(10-ethyl-phenothiazine-3-methylidene)*p,p'*-diamino-1,2-diphenylethane **2.**
^{1}H-RMN δ(ppm) 2.94(s, 4H), 7.17(m, 6H), 7.11(m, 6H), 8.31(s, 2H), 7.65(d, 2H), 7.62(dd, 2H), 7.16, 6.93(t, 2H), 6.88(d, 2H), 6.89(d, 2H), 1.44(t, 6H), 3.96(q, 4H).
^{13}C-RMN δ(ppm) 12.9, 37.5, 158.2, 115.2, 114.6, 121.9, 129.2, 123.6, 124.5, 122.9, 127.4, 127.4, 127.1, 128.5, 130.9, 143.9, 147.8, 150.0, 139.3, 42.1.
SM (m/e) 686

N,N'-bis(10-ethyl-phenothiazine-3-methylidene)*p,p'*-diaminodiphenylether **3.**
^{1}H-RMN δ(ppm) 7.04(d, 4H), 7.20(d, 4H), 8.33(s, 2H), 7.66(d, 2H), 7.37(dd, 2H), 7.15(td, 2H), 7.11(dd, 2H), 6.92(t, 2H), 6.88(d, 2H), 6.89(d, 2H), 1.44(t, 6H), 3.97(q, 4H)
^{13}C-RMN δ(ppm) 15.9, 42.2, 157.9, 115.2, 114.6, 122.2, 119.4, 123.8, 124.5, 122.9, 127.4, 127.4, 127.1pp, 128.5, 130.7, 143.8, 147.5, 147.4, 155.5.
SM (m/e) 674

N,N'-bis(10-methyl-phenothiazine-3-methylidene)*p,p'*-diaminodiphenylmethane **4.**
^{1}H-RMN δ(ppm) 4.00(s, 2H), 7.20(d, 4H), 7.14(m, 6H), 8.32(s, 2H), 7.69(d, 2H), 7.63(dd, 2H), 7.20(t, 2H), 6.95(t, 2H), 6.84(d, 2H), 6.83ppn(d, 2H), 3.42(s, 6H).
^{13}C-RMN δ(ppm) 35.6, 40.9, 158.3, 114.4, 113.4, 121.0, 129.6, 122.9., 123.9, 123.0, 127.2, 127.5, 126.8, 128.8, 130.9, 144.8, 148.3, 150.1, 138.8
SM (m/e) 644

N,N'-bis(10-methyl-phenothiazine-3-methylidene)*p,p'*-diamino-1,2-diphenylethane **5.**
^{1}H-RMN δ(ppm) 2.94(s, 4H), 7.17(m, 8H), 7.12(d, 4H), 8.33(s, 2H), 7.70(d, 2H), 7.64(dd, 2H), 6.96(t, 2H), 6.85(d, 2H), 6.84(d, 2H), 3.42(s, 6H)
^{13}C-RMN δ(ppm) 35.6, 37.5, 158.2, 114.4, 113.8, 120.9, 129.2, 123.0, 126.8, 127.2, 127.5, 128.8
SM (m/e) 658

N,N'-bis(10-methyl-phenothiazine-3-methylidene)*p,p'*-diaminodiphenylether **6.**
^{1}H-RMN δ(ppm) 7.05(d, 4H), 7.21(d, 4H), 8.34(s, 2H), 7.07(d, 2H), 7.64(dd, 2H), 7.18(td, 2H), 7.14(dd, 2H), 6.95(t, 2H), 6.84(d, 2H), 6.85(d, 2H), 3.42(s, 6H)
^{13}C-RMN δ(ppm) 400MHz, solvent $CDCl_3$.
35.6, 158.0, 114.4, 113.8, 122.2, 119.4, 122.8, 123.9, 123.0, 127.2, 127.5, 126.8, 128.8, 130.9, 144.8, 148.3, 147.3, 155.5.
SM (m/e) 646

N-(10-methyl-phenothiazine-3-methylidene)5-amino-3-methyl-1-phenylpyrazol **7.**
^{1}H-RMN δ(ppm) 8.46(s, H), 7.60(s, 1H), 7.59(d, 1H), 7.17(td, 1H), 7.13(dd, 1H), 6.96(td, 1H), 6.82(d, 1H), 6.81(d, 1H), 3.03(s, 3H), 2.35(s, 3H), 6.12(s, 1H), 7.44(t, 2H), 7.73(d, 2H), 7.30(t, 1H)
^{13}C-RMN δ(ppm) 14.2, 35.6, 158.7, 93.0, 124.0, 128.5, 126.3, 127.6, 123.2, 127.2, 129.3, 127.0, 148.9, 144.5, 113.8, 114.5, 122.6, 123.6, 139.5, 150.6, 130.4, 149.1.
SM (m/e) 396

N-(10-methyl-phenothiazine-3-methylidene) 5-amino-3-methyl-1-(*p*-nitrophenyl)pyrazol **8.**
^{1}H-RMN δ(ppm) 8.42(s, 1H), 7.62(s, 1H), 7.64(d, 1H), 7.02(td, 1H), 7.14(dd, 1H), 6.98(td, 1H), 6.84(d, 1H), 6.87(d, 1H), 3.43(s, 3H), 2.35(s, 3H), 6.15(s, 1H), 8.31(dt, 2H), 8.09(dt, 2H).
^{13}C-RMN δ(ppm) 14.2, 35.7, 159.9, 94.5, 124.3, 122.9, 159.9, 127.6, 123.4, 127.2, 129.8, 127.3, 149.5, 144.4, 114.0, 114.6, 122.5, 124.2, 144.7, 151.8, 129.8, 150.9.
SM (m/e) 441

Conclusions

The condensation reaction of 3-formyl-10-alkyl-phenothiazine with aromatic diamines in alcohol is characterised by moderate reaction time and good yields; microwave activation of this condensation reaction reduces the reaction time.

The *E* configuration for the geometric isomers of the azomethine group is supported by 2D-NMR spectrum. *Z* configuration isomers appear after photochemical reactions in polar solvent, upon visible light exposure. UV light exposure of the Schiff bases in polar solvent induces the decomposition to the corresponding formyl derivatives.

The low intensity absorption band situated at 520 nm in the UV-Vis absorption spectrum of *N*-(10-alkyl-phenothiazine-3-methylidene)benzenamine derivatives can be used in the identification of this chromophore system.

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