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SYNTHESIS OF SOME NEW DIALDEHYDES AND DIMETHANOLS INCORPORATING PHENOTHIAZINE UNITS

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ABSTRACT. The synthesis of some new dialdehydes with 10*H*-phenothiazine units and of their corresponding dimethanols is reported. NMR investigations fully supported the assigned structures.

Keywords: *phenothiazine, dialdehydes, dialcohols, Suzuki cross-coupling reactions*

INTRODUCTION

Phenothiazine is an important electron rich nitrogen-sulphur heterocyclic motif with a broad pharmacological activity, the phenothiazine core being found in tranquilizers, antipyretics, antihelmitics, antituberculotics or antihistamines [1]. Phenothiazines possess good donor abilities, hence a low oxidation potential, forming easily radical cations [2]. Thus, the "butterfly" dynamic structure of the tricyclic phenothiazine skeleton becomes, upon oxidation to the radical cation, a rigid planar one [3].

In the recent years, due to its interesting electronic properties phenothiazine became intensively used as a redox active unit in material sciences [4], biology and biochemistry and as a marker for biochemical systems such as proteins or DNA [5]. Müller *et al* investigated and incorporated phenothiazine units in various systems like cruciform fluorophores [6], phenothiazophanes [7], molecular wires [8] and ligands for surface modification [9].

In previous works, we studied phenothiazine compounds possessing thioacetate or mercapto groups as adsorbates on gold surfaces [10]. Their behavior as ligands for SAMs formation was also investigated using computational methods [11].

We report herein the synthesis and structural assignment of some new dialdehydes and of their corresponding dimethanols incorporating phenothiazine units.

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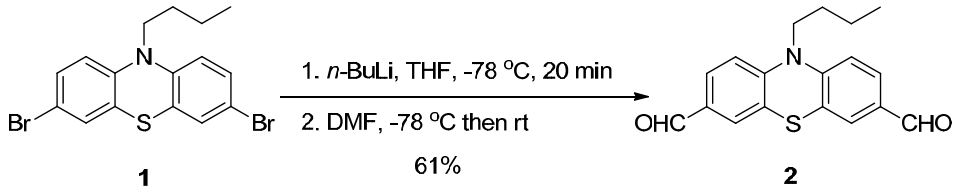
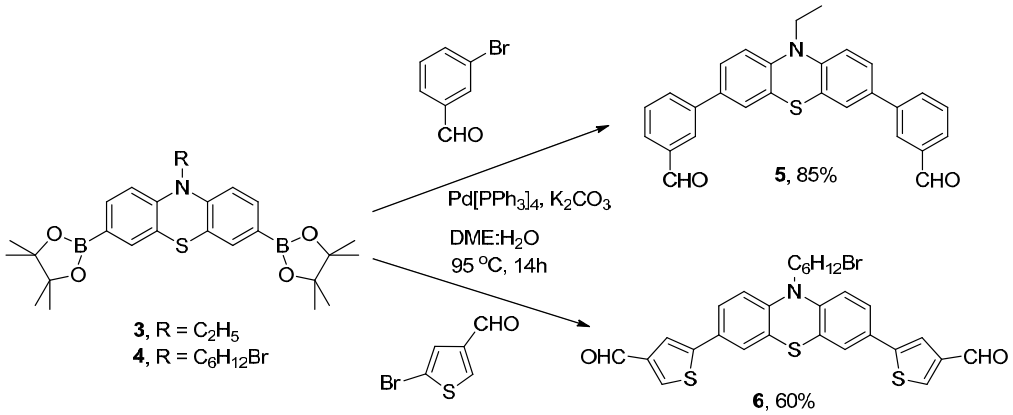
RESULTS AND DISCUSSIONS

Dialdehyde **2** was obtained starting from dibromophenothiazine **1** which first reacted in a lithium-bromine interchange, followed by the trapping of the dilithiated form of **1** with dimethylformamide as electrophile [12] (Scheme 1).



Scheme 1

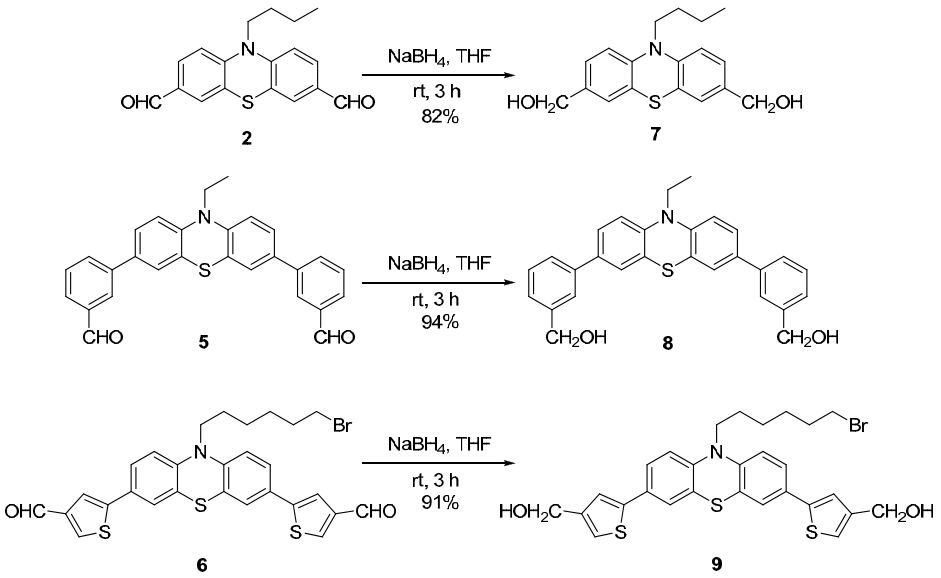
The synthesis of dialdehydes **5** and **6** was accomplished by Suzuki cross-coupling reactions. Therefore, suitable phenothiazine pinacolyl boronic esters (**3** and **4**) [10, 13b] reacted with appropriate commercially available halogenated formyl derivatives under Suzuki cross-coupling conditions (potassium carbonate as a base, tetrakis(triphenylphosphine) palladium as the catalyst [13], and a mixture of dimethoxyethane and water as solvent) and gave dialdehydes **5** and **6** in fair to good yields (Scheme 2).



Scheme 2

The synthesized dialdehydes are suitable starting materials for the synthesis of dialcohols. By reducing the dialdehydes **2**, **5** and **6** with sodium borohydride in tetrahydrofurane, following a procedure adapted form the literature [14], the corresponding dimethanols **7**-**9** were obtained in good yields (Scheme 3).

NMR analyses fully confirmed the structure of targeted compounds **2**, **5**-**9**. Besides the normally expected signals of the phenothiazine core, the typical ^{1}H and ^{13}C resonances of formyl and hydroxymethyl groups were found throughout in the discussed series. These NMR data are collecterd in Table 1.



Scheme 3

Table 1. Relevant NMR data (DMSO-d_6, δ, ppm) for compounds **2** and **5-9**.

Compd.	^{1}H			^{13}C	
	C*H*O	C*H*$_2$OH	CH$_2$O*H*	CHO	CH$_2$OH
2	9.80	-	-	190.6	-
5	10.08	-	-	193.2	-
6	9.84	-	-	186.0	-
7	-	4.37	5.10	-	62.1
8	-	4.56	5.25	-	62.8
9	-	4.45	5.16	-	59.0

Upon reduction of the aldehydes with the formation of the corresponding dialcohols, the essential difference in the NMR spectra is the appearance of the signals corresponding to the alcohol group. The methylenic protons appear as dublet signals at 4.37 for **7**, 4.56 for **8** and 4.45 for **9** while the hydroxylic protons appear as triplet signals at 5.10, 5.25 and 5.16 respectively. The ^{13}C-NMR spectra of the alcohols exhibit also the characteristic shifts for the carbon atom in alcohol newly formed (62.1 for **7**, 62.8 for **8** and 59.0 for **9**).

CONCLUSIONS

New dialdehydes (**2**, **5** and **6**) with phenothiazine units were obtained in good yields (60-85 %) either by Suzuki cross-coupling reactions (**5** and **6**) or by DMF trapping by the corresponding dilithiated phenothiazine (**2**). The sodium borohydride reduction of the dialdehydes (**2**, **5** and **6**) furnished in good yields (82-94 %) the corresponding dimethanol derivatives (**7**-**9**).

EXPERIMENTAL SECTION

General

^{1}H NMR (300 or 400 MHz) and ^{13}C NMR (75 or 100 MHz) spectra were recorded in DMSO-d_6 on Bruker spectrometers. ESI MS were recorded on Agilent 6320 ion trap spectrometer in positive mode. Melting points were measured with Kleinfeld Apotec melting point apparatus and they are uncorrected. Thin layer chromatography (TLC) was carried out on aluminium sheets coated with silica gel 60 F_{254} using UV visualization.

Synthesis of derivative 2

A solution of 3,7-dibromo-10-*n*-buthyl-10*H*-phenothiazine (4 mmol) in dry tetrahydrofurane (50 mL) was cooled to -78 °C. Then *n*-BuLi (solution 2.5 M in hexane, 12.8 mmol) was added dropwise for 20 minutes. The reaction mixture was stirred 30 minutes at -78 °C and then dry dimethylfomamide (10 mmol) was added dropwise. After electrophile addition, the cooling bath was removed and the reaction mixture was let to reach the room temperature. Water (50 mL) and diethyl ether (100 mL) were added and the organic layer was separated. The aqueous phase was washed three times with small portions of diethyl ether (3x20 mL) and the combined organic layers were dried over sodium sulphate. After filtering, the solvents were removed in vacuo and the residue was chromatographed on silica gel (dichloromethane / pentane = 4 / 1) to yield 0.76 g (2.46 mmol, 61%) of **2** as an orange solid.

*10-n-buthyl-3,7-diformyl-10H-phenothiazine **2**.* Orange solid, m.p. = 92.4 – 93.2 ºC, yield 61%. Calculated for $C_{18}H_{17}NO_2S$ (311.10): C, 69.43; H, 5.50; N, 4.50; S, 10.30. Found: C, 69.57; H, 5.41; N, 4.66; S, 10.42. ^{1}H NMR (300 MHz, DMSO-d_6, δ ppm): 0.87 (3H, t, *J* = 7.2 Hz), 1.40 (2H, m), 1.67 (2H, m), 3.99 (2H, t, *J* = 6.9 Hz), 7.22 (2H, d, J = 8.4 Hz), 7.60 (2H, d, *J* = 1.5 Hz), 7.73 (2H, dd, *J* = 8.4 Hz, *J* = 1.8 Hz), 9.80 (2H, s). ^{13}C NMR (75 MHz, DMSO-d_6, δ ppm): 13.4 (CH_3), 19.1 (CH_2), 28.0 (CH_2), 47.0 (CH_2), 116.3 (CH), 122.8 ($C_{quat.}$), 127.8 (CH), 130.1 (CH), 131.6 ($C_{quat.}$), 148.2 ($C_{quat.}$), 190.6 (CH).

MS (ESI) m/z = *312.3 $[M+H]^+$*.

General procedure for synthesis of derivatives 5 and 6

Into a mixture of phenothiazine diboronic-diester (**3** or **4**, 2 mmol), potassium carbonate (20 mmol), the appropriate bromoaldehyde (*m*-bromo-benzaldehyde or 3-formyl-5-bromo-thiophene, 4.4 mmol) and solvents [dimethoxy-ethane / distilled water (2 : 1; 90 mL)] argon was purged for 20 minutes. Then, the catalyst tetrakis[triphenylphosphine] palladium (0.2 mmol) was added. The reaction mixture was refluxed for 14 hours. After cooling at room temperature, dichloromethane (200 mL), water (50 mL) and Na_2SO_3 oversaturated solution (50 mL) were added to the reaction mixture and the organic phase was separated. The aqueous layer was extracted three times with small amounts of dichloromethane (3x20 mL). The combined organic layers were dried over sodium sulphate, the solvents were removed in vacuo and the residue was chromatographied on silica gel (dichloromethane / pentane.= 4 / 1)

10-ethyl-3,7-bis(3'-formylphenyl)-10H-phenothiazine ***5.*** Yellow solid, m.p. = 123.8-125.0 ºC, yield 85%. Calculated for $C_{28}H_{21}NO_2S$ (435.13): C, 77.21; H, 4.86; N, 3.22; S, 7.36. Found: C, 77.03; H, 4.75; N, 3.40; S, 7.48. ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 1.36 (3H, t, *J* = 6.8 Hz), 4.01 (2H, q), 7.15 (2H, d, *J* = 8.4 Hz), 7.56 (2H, s), 7.60 (2H, d, *J* = 8.4 Hz), 7.66 (2H, t, *J* = 7.6 Hz), 7.84 (2H, d, *J* = 7.2 Hz), 8.00 (2H, d, *J* = 7.6 Hz), 8.19 (2H, s), 10.08 (2H, s). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 12.4 (CH_3), 41.2 (CH_2), 115.6 (CH), 122.9 ($C_{quat.}$), 124.9 (CH), 126.0 (CH), 127.3 (CH), 127.5 (CH), 129.7 (CH), 131.8 (CH), 132.9 ($C_{quat.}$), 136.7 ($C_{quat.}$), 139.5 ($C_{quat.}$), 143.5 ($C_{quat.}$), 193.2 (CH).

MS (ESI) m/z = *436.2 [M+H]$^+$.*

10-(6'-bromohexyl)-3,7-bis(4"-formyl-thiophen-2"-yl)-10H-phenothiazine ***6.*** Yellow solid, m.p. = 49.1 – 51.0 ºC, yield 60%. Calculated for $C_{28}H_{24}BrNO_2S_3$ (581.02): C, 57.72; H, 4.15; N, 2.40; Br, 13.72; S, 16.51. Found: C, 57.61; H, 4.33; N, 2.27; Br, 13.88; S, 16.51. ^{1}H NMR (300 MHz, DMSO-d_6, δ ppm): 1.39 (4H, overlapped peaks), 1.67-1.77 (2H, overlapped peaks), 3.47 (2H, t, *J* = 6.6 Hz), 3.89 (2H, t, *J* = 6.6 Hz), 7.03-7.06 (2H, m), 7.51-7.53 (4H, overlapped peaks), 7.76 (2H, s), 8.53 (2H, s), 9.84 (2H, s). ^{13}C NMR (75 MHz, DMSO-d_6, δ ppm): 25.1 (CH_2), 25.8 (CH_2), 27.0 (CH_2), 32.0 (CH_2), 34.9 (CH_2), 46.5 (CH_2), 116.1 (CH), 119.4 (CH), 123.6 ($C_{quat.}$), 124.0 (CH), 125.2 (CH), 127.2 ($C_{quat.}$), 137.7 (CH), 143.4 ($C_{quat.}$), 143.9 ($C_{quat.}$), 144.3 ($C_{quat.}$), 186.0 (CH).

MS (ESI) m/z = *582.2 [M+H]$^+$.*

General procedure for synthesis of derivatives 7-9

A solution of dialdehyde (**2**, **5** or **6**; 1 mmol) in 40 ml THF was added dropwise to a suspension of $NaBH_4$ (7 mmol) in water (20 mL). The reaction mixture was stirred for 3h at room temperature and then poured in a 1 / 1 mixture of water and ethyl acetate (200 mL). The organic layer was separated and the aqueous phase was extracted three times more with small portions

of ethyl acetate (3x20mL). The combined organic layers were dried over $MgSO_4$. The solvents were evaporated *in vacuo* and the residue was purified by column chromatography (ethyl acetate / pentane = 1 / 2).

10-n-buthyl-3,7-bis(hydroxymethyl)-10*H*-phenothiazine ***7.*** Yellow solid, m.p. = 92.4-93.2ºC, yield 82 %. Calculated for $C_{18}H_{21}NO_2S$ (315.13): C, 68.54; H, 6.71; N, 4.44; S, 10.17. Found: C, 68.39; H, 6.54; N, 4.31; S, 10.02. ^{1}H NMR (300 MHz, DMSO-d_6, δ ppm): 0.85 (3H, t, *J* = 7.5 Hz), 1.56 (2H, m), 1.63 (2H, m), 3.83 (2H, t, *J* = 6.6 Hz), 4.37 (4H, d, *J* = 5.7 Hz), 5.1 (2H, t, J = 5.7 Hz), 6.93-6.95 (2H, overlapped peaks), 7.06-7.12 (4H, overlapped peaks). ^{13}C NMR (75 MHz, DMSO-d_6, δ ppm): 13.6 (CH_3), 19.3 (CH_2), 28.3 (CH_2), 46.0 (CH_2), 62.1 (CH_2), 115.2 (CH), 123.1 ($C_{quat.}$), 125.2 (CH), 125.8 (CH), 136.5 ($C_{quat.}$), 143.4 ($C_{quat.}$).

MS (ESI) m/z = 316.1 [M+H]$^+$.

10-ethyl-3,7-bis(3'-hydroxymethylphenyl)-10H-phenothiazine ***8.*** White solid, m.p. = 149.6- 151.5 ºC, yield 94 %. Calculated for $C_{28}H_{25}NO_2S$ (439.16): C, 76.51; H, 5.73; N, 3.19; S, 7.29. Found: C, 76.68; H, 5.52; N, 3.02; S, 7.44. ^{1}H NMR (400 MHz, DMSO-*d_6*, δ ppm): 1.36 (3H, t, *J* = 6.4 Hz), 3.95 (2H, q), 4.56 (4H, d, *J* = 5.6 Hz), 5.25 (2H, t, J = 5.6 Hz), 7.07 (2H, d, *J* = 8.4 Hz), 7.27 (2H, d, *J* = 7.2 Hz), 7.37 (2H, t, *J* = 7.0 Hz), 7.43 (2H, s), 7.48 (4H, d, *J* = 8.4 Hz), 7.57 (2H, s). ^{13}C NMR (75 MHz, DMSO-*d_6*, δ ppm): 12.5 (CH_3), 41.1 (CH_2), 62.8 (CH_2), 115.5 (CH), 122.8 ($C_{quat.}$), 123.9 (CH), 124.2 (CH), 124.7 (CH), 125.1 (CH), 125.7 (CH), 128.6 (CH), 134.3 ($C_{quat.}$), 138.5 ($C_{quat.}$), 143.16 ($C_{quat.}$), 143.19 ($C_{quat.}$).
MS (ESI) *m/z* = 440.3 [M+H]$^+$

10-(6'-bromohexyl)-3,7-bis(4"-hydroxymethyl-thiophene-2"yl)-10H-phenothiazine ***9.*** Green solid, m.p.=110.9-112.5 ºC, yield 91%. Calculated for $C_{28}H_{28}BrNO_2S_3$ (585.05): C, 57.33; H, 4.81; N, 2.39; Br, 13.62; S, 16.40. Found: C, 57.51; H, 4.69; N, 2.26; Br, 13.48; S, 16.51. ^{1}H NMR (300 MHz, DMSO-*d_6*, δ ppm): 1.39-1.40 (4H, overlapped peaks), 1.68-1.77 (2H, overlapped peaks), 3.47 (2H, t, *J* = 6.6 Hz), 3.86 (2H, t, *J* = 6.6 Hz), 4.45 (4H, d, *J* = 5.7 Hz), 5.16 (2H, t, *J* = 5.7 Hz), 7.02 (2H, d, *J* = 8.4 Hz), 7.21 (2H, s), 7.33 (2H, s), 7.38-7.43 (4H, overlapped peaks), 7.76 (2H, s), 8.53 (2H, s), 9.84 (2H, s). ^{13}C NMR (75 MHz, DMSO-*d_6*, δ ppm): 25.1 (CH_2), 25.8 (CH_2), 27.0 (CH_2), 32.1 (CH_2), 34.9 (CH_2), 46.4 (CH_2), 59.0 (CH_2), 116.0 (CH), 119.8 (CH), 122.6 (CH), 123.4 (CH), 123.5 ($C_{quat.}$), 124.5 (CH), 128.5 ($C_{quat.}$), 142.1 ($C_{quat.}$), 143.3 ($C_{quat.}$), 145.6 ($C_{quat.}$).
MS (ESI) *m/z* = 586.1 [M+H]$^+$

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