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Baker's yeast mediated preparation of (10-alkyl-10*H*-phenothiazin-3-yl)methanols

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Abstract

A series of 10-alkyl-10*H*-phenothiazine-3-carbaldehydes (**2a**–**h**) were obtained by Vilsmeier–Haack formylation from the corresponding 10-alkyl-10*H*-phenothiazines (**1a**–**h**) and reduced to (10-alkyl-10*H*-phenothiazine-3-yl)methanols (**3a**–**h**) by two alternative methods. The baker's yeast catalyzed reaction proved to be superior over the $NaBH_4$ reduction and yielded the desired 3-hydroxymethylphenothiazines (**3a**–**h**) almost quantitatively. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: *N*-alkylphenothiazines; Formylation; Aldehydes; Reduction; Baker's yeast

1. Introduction

Phenothiazines are important as psyhotropic compunds primarily, but they have various other biological activities [1–3], too. This heterocyclic system is also interesting from synthetic point of view [1–4]. The ring skeleton of phenothiazines—two carbacyclic aromatic rings connected to each other via a sulfide and an imino bridge—allows several types of reactions, such as nucleophilic substitution at the nitrogen [2], electrophilic substitution at the aromatic rings [2], oxidation at the sulfur, formation of stable cation-radicals from the whole ring system [5], photochemical reactions [2], etc.

The classical way to phenothiazines is the cyclization of substituted diphenylamines and sulfur at high temperature [6]. By this approach only limited types of substituted phenothiazines could be prepared, usually in moderate yields via tedious work-up.

Another approach is the substitution of the aromatic rings of unsubstituted phenothiazines by different moieties. The position and number of substituents which can be introduced in this way depends strongly on the moiety present at the nitrogen of the phenothiazine ring system. Electrophilic substitution of the unsubstituted phenothiazine provided generally the 3,7-disubstituted compounds [2] but using strong electrophiles resulted even higher degree of substitution [7]. Electrophilic substitution on the *N*-alkylphenothiazines resulted usually the corresponding 3-substituted compounds [8], but in some

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cases the 3,7-disubstituted derivatives were formed [11]. Electrophilic substitution on phenothiazines bearing electron-withdrawing substituent at the nitrogen required strong electrophiles and proceeded with formation of 2-substituted or 2,8-disubstituted compounds [9–11].

The various reactions of 10-methyl-10*H*-phenothiazine-3-carbaldehyde (**2a**) with aliphatic, aromatic and heterocyclic amines, hydrazines, semicarbazides [12,13] or with activated methylene group-containing compounds [14,15]; or the transformation of (10-methyl-10*H*-phenothiazine-3-yl)methanol (**3a**) into the corresponding 3-bromomethylphenothiazine [16] demonstrate the synthetic usefulness of the 3-formyl- and 3-hydroxymethylphenothiazines.

There are scattered examples for preparation of 10-alkyl-10*H*-phenothiazine-3-carbaldehydes (**2**), which were obtained from *N*-alkyl-10*H*-phenothiazines (**1**) with *N*-methyl-*N*-phenyl-formamide/$POCl_3$ [17,18] or with *N*,*N*-dimethylformamide/$POCl_3$ (Vilsmeier–Haack method) [15] or synthesized from 3-bromo-10-methyl-10*H*-phenothiazine and *N*,*N*-dimethylformamide via organolithium intermediate [19].

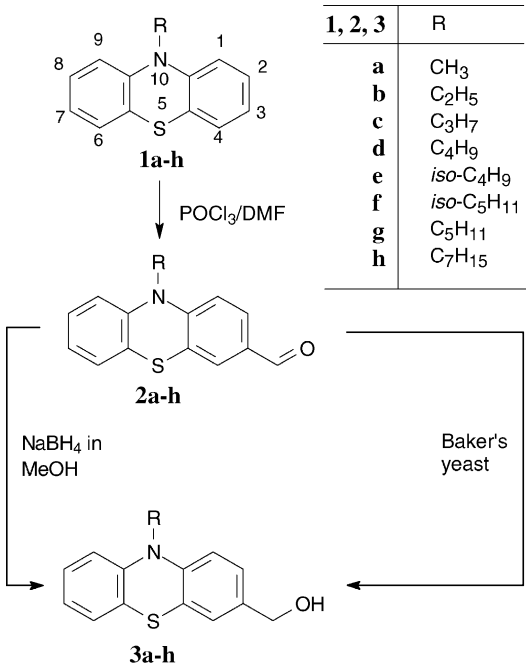

Fig. 1. Preparation and reduction of 10-alkyl-10*H*-phenothiazine-3-carbaldehydes (**2a**–**h**).

The only example for preparation of (10-alkyl-10*H*-phenothiazine-3-yl)methanols (**3**) is the reduction of 10-methy-10*H*-phenothiazine-3-carbaldehyde (**2a**) by $LiAlH_4$ in diethyl ether [20].

The various biological activities of phenothiazine derivatives [1–3] inspired us to develop synthetic methods for preparation of new phenothiazine derivatives bearing formyl and hydroxymethyl moieties—which can be easily extended by condensation, acylation or substitution reactions—in the C3 position of the ring system. Synthesis of a series of 10-alkyl-10*H*-phenothiazine-3-carbaldehydes (**2a**–**h**) and their chemical and biocatalytic reduction into the corresponding (10-alkyl-10*H*-phenothiazine-3-yl)methanols (**3a**–**h**) under mild conditions is described in this paper (Fig. 1).

2. Experimental

2.1. Materials and methods

Phenothiazine, reagents and solvents were products of Aldrich or Fluka. Amberlite XAD-7 nonionic polymeric adsorbent was obtained from Aldrich (catalogue number 21,649-6). Baker's yeast as wet cake was obtained from Budafok Ltd., Hungary. The ^1H and ^{13}C NMR spectra were recorded on a Brucker DRX-500 spectrometer operating at 500 and 125 MHz, respectively. Chemical shifts are expressed in ppm values from TMS as internal standard. IR spectra were recorded on a Specord 2000 spectrometer. Mass spectra were taken on a VG QUATTROO mass spectrometer in $M + H^+$ ES and ES modes. Preparative chromatographic separations were performed using vacuum chromatography [21] on Merck Kieselgel 60 (0.063–0.200 μm). Melting points were determined by hot plate method and are uncorrected. All solvents were purified and dried by standard methods as required.

2.2. Vilsmeier–Haack formylation of 10-alkyl-10H-phenothiazines (*1a–h*)

To ice-cooled dimethylformamide (30 ml) phosphorus oxychloride (10 ml) was added dropwise, followed by addition of 10-alkyl-10*H*-phenothiazine (**1a**–**h**, 100 mmol). The resulting mixture was stirred

Table 1
Yields and analytical data for 10-alkyl-10*H*-phenothiazine-3-carbaldehydes (**2a**–**h**)

Product	Yield (%)	Melting point[a] (Lit.) (°C)	Formula	HRMS (M^+ calculated/found)	MS (*m*/*z*)
2a	52	84 (88–89 [22])	$C_{14}H_{11}NOS$	242.0640/242.0643	243, 242, 241, 215, 214, 213, 212, 201, 200, 199, 198, 181, 180
2b	48	98 (101–102 [22])	$C_{15}H_{13}NOS$	256.0796/256.0785	257, 256, 255, 229, 228, 227, 226, 200, 199, 198, 181, 180
2c	47	45	$C_{16}H_{15}NOS$	270.0953/270.0955	271, 270, 269, 243, 241, 240, 229, 228, 227, 226, 212, 208, 200, 199, 198
2d	49	54–55	$C_{17}H_{17}NOS$	284.1109/284.1109	285, 284, 283, 257, 256, 255, 242, 241, 240, 229, 228, 227, 226, 212, 208, 201, 200, 199, 198
2e	50	64.5	$C_{17}H_{17}NOS$	284.1109/284.1109	285, 284, 283, 257, 256, 255, 241, 240, 230, 229, 228, 227, 212, 201, 200, 199, 198
2f	46	77	$C_{18}H_{19}NOS$	298.1266/298.1263	299, 298, 297, 271, 270, 269, 241, 240, 229, 228, 227, 226, 212, 200, 199, 198
2g	48	81–81.5	$C_{18}H_{19}NOS$	298.1266/298.1263	299, 298, 297, 271, 270, 269, 241, 240, 229, 228, 227, 226, 212, 200, 199, 198
2h	49	38	$C_{20}H_{23}OS$	326.1579/326.1577	327, 326, 325, 298, 297, 241, 240, 227, 226, 212, 200, 198

[a] Solvent for recrystallization: EtOH for **2a**,**b**; hexane for **2c**–**h**.

at 100 °C for 2 h and then poured into 500 g of ice. The pH value of the mixture was set to 6 by addition of saturated aqueous NaOAc solution and it was extracted with toluene (200 ml, four times). The combined toluene solutions were dried over anhydrous Na_2SO_4, then concentrated to a volume of 50 ml by distillation under reduced pressure. Chromatography on silica gel using toluene as eluent followed by recrystallization from ethanol or hexane resulted the formyl derivatives (**2a**–**h**) as yellow solids. Yields, and analytical data for the 10-alkyl-10*H*-phenothiazine-3-carbaldehydes (**2a**–**h**) are shown in Tables 1 and 2. Physical constants and spectra for the known 10-methyl (**2a**) [22,23] and 10-ethyl (**2b**) [22,24] derivatives agreed well with those
reported.

*2.3. Reduction of 10-alkyl-10H-phenothiazine-3-carbaldehydes (**2a**–**h**) with sodium tetrahydridoborate (method A)*

To a stirred solution of the formyl derivative (**2a**–**h**, 1 mmol) in dry methanol (5 ml) $NaBH_4$ (1 mmol) was added portionwise at RT and the resulting mixture was stirred further at RT for the time given in Table 3 (disappearance of the yellow color of the solution indicated the completeness of the reduction). After the reduction was completed, the mixture was quenched by dropwise addition of 2 N HCl solution (1 ml) and evaporated to a final volume of about 1 ml. To this residue water (3 ml) and CH_2Cl_2 (6 ml) was added. After separating the two layers, the aqueous layer was extracted with CH_2Cl_2 (6 ml). The combined organic layers were dried over anhydrous $MgSO_4$ and the solvent was removed. The residue was purified by column chromatography on silica gel using toluene–acetone (9:1) as eluent yielding the 3-hydroxymethyl-phenothiazines (**3a**–**h**). Yields and analytical data for the (10-alkyl-10*H*-phenothiazine-3-yl)methanols (**3a**–**h**) are shown in Tables 3 and 4.

*2.4. Reduction of 10-alkyl-10H-phenothiazine-3-carbaldehydes (**2a**–**h**) with baker's yeast (method B)*

To a stirred (250 rpm) suspension of 25 g fresh baker's yeast in 250 ml water, a solution of the formyl derivative (**2a**–**h**, 40 mmol) in ethanol (10 ml) was added dropwise at RT and the resulting mixture was stirred further at RT for the time given in Table 3 (although disappearance of the yellow color of the solution was also indicative here, progress of the reaction was checked by TLC on silica gel plates using

Table 2
Spectral data for 10-alkyl-10*H*-phenothiazine-3-carbaldehydes (**2a–h**)

Product	IR (KBr) ν (cm^{-1})	^1H NMR ($CDCl_3$)[a] δ (ppm), J (Hz)	^{13}C NMR ($CDCl_3$)[a] δ (ppm)
2a	1676, 1600, 1568, 1464, 1396, 1380, 1328, 1256, 1204, 752	3.32 (3H, s, $H_{C1'}$), 6.70 (2H, m, H_{C1} and H_{C9}), 6.93 (1H, t, H_{C7}), 7.06 (1H, d, H_{C6}), 7.13 (1H, m(t), H_{C8}), 7.49 (1H, dd, H_{C4}), 7.56 (1H, dd, H_{C2}), 9.74 (1H, s, CHO)	35.71 ($C_{1'}$), 113.64 (C_1), 114.75 (C_9), 122.35 (C_7), 123.60 (C_{6a}), 125.83 (C_{4a}), 127.16 (C_8), 127.68 (C_6), 127.73 (C_4), 130.44 (C_2), 131.03 (C_3), 143.92 (C_{9a}), 150.87 (C_{1a}), 189.90 (C_{CHO})
2b	1672, 1600, 1576, 1468, 1400, 1368, 1324, 1256, 1240, 1200, 756	1.38 (3H, t, $H_{C2'}$), 3.89 (2H, q, $H_{C1'}$), 6.83 (2H, m, H_{C1} and H_{C9}), 6.91 (1H, t, H_{C7}), 7.03 (1H, d, H_{C6}), 7.11 (1H, m(t), H_{C8}), 7.49 (1H, dd, H_{C4}), 7.55 (1H, dd, H_{C2}), 9.73 (1H, s, CHO)	12.74 ($C_{1'}$), 42.37 ($C_{2'}$), 114.28 (C_1), 115.52 (C_9), 123.01 (C_7), 123.45 (C_{6a}), 124.22 (C_{4a}), 127.20 (C_8), 125.80 (C_6), 127.70 (C_4), 130.18 (C_2), 130.86 (C_3), 142.85 (C_{9a}), 150.05 (C_{1a}), 189.92 (C_{CHO})
2c	1672, 1596, 1576, 1464, 1440, 1364, 1288, 1248, 1240, 1200, 744	0.98 (3H, t, $H_{C3'}$), 1.79 (2H, m, $H_{C2'}$), 3.80 (2H, t, $H_{C1'}$), 6.82 (2H, m, H_{C1} and H_{C9}), 6.91 (1H, t, H_{C7}), 7.05 (1H, d, H_{C6}), 7.11 (1H, m(t), H_{C8}), 7.51 (1H, dd, H_{C4}), 7.56 (1H, dd, H_{C2}), 9.74 (1H, s, CHO)	11.13 ($C_{3'}$), 20.07 ($C_{3'}$), 49.68 ($C_{1'}$), 114.75 (C_1), 115.96 (C_9), 123.52 (C_7), 123.65 (C_{6a}), 124.86 (C_{4a}), 127.43 (C_6), 127.52 (C_8), 128.13 (C_4), 130.05 (C_2), 130.94 (C_3), 143.26 (C_{9a}), 150.56 (C_{1a}), 189.84 (C_{CHO})
2d	1676, 1600, 1576, 1564, 1472, 1448, 1440, 1368, 1252, 1228, 1200, 752	0.93 (2H, t, $H_{C4'}$), 1.44 (2H, m, $H_{C3'}$), 1.77 (2H, m, $H_{C2'}$), 3.86 (2H, t, $H_{C1'}$), 6.86 (2H, m, H_{C1} and H_{C9}), 6.94 (1H, t, H_{C7}), 7.08 (1H, d, H_{C6}), 7.14 (1H, m(t), H_{C8}), 7.54 (1H, dd, H_{C4}), 7.61 (1H, dd, H_{C2}), 9.76 (1H, s, CHO)	13.72 ($C_{4'}$), 20.02 ($C_{3'}$), 28.82 ($C_{2'}$), 47.65 ($C_{1'}$), 114.79 (C_1), 115.96 (C_9), 123.55 (C_7), 123.79 (C_{6a}), 124.99 (C_{4a}), 127.52 (C_6), 127.55 (C_8), 128.26 (C_4), 130.06 (C_3), 131.01 (C_3), 143.37 (C_{9a}), 150.73 (C_{1a}), 189.92 (C_{CHO})
2e	1692, 1592, 1584, 1568, 1464, 1372, 1232, 1204, 744	0.96 (6H, d, $H_{C3'}$), 2.16 (1H, m, $H_{C2'}$), 3.86 (2H, d, $H_{C1'}$), 6.85 (2H, m, H_{C1} and H_{C9}), 6.94 (1H, t, H_{C7}), 7.10 (1H, d, H_{C6}), 7.15 (1H, m(t), H_{C8}), 7.55 (1H, dd, H_{C4}), 7.59 (1H, dd, H_{C2}), 9.76 (1H, s, CHO)	19.96 ($C_{3'}$), 25.55 ($C_{2'}$), 55.40 ($C_{1'}$), 115.47 (C_1), 116.60 (C_9), 123.57 (C_7), 124.72 (C_{6a}), 125.98 (C_{4a}), 127.45 (C_8), 127.66 (C_6), 128.53 (C_4), 129.81 (C_2), 131.07 (C_3), 143.88 (C_{9a}), 151.32 (C_{1a}), 189.90 (C_{CHO})
2f	1676, 1600, 1576, 1552, 1468, 1440, 1364, 1252, 1200, 748	0.94 (6H, d, $H_{C4'}$), 1.66–1.72 (2H, m, $H_{C2'}$), 1.72–1.78 (1H, m, $H_{C3'}$), 3.88 (2H, t, $H_{C1'}$), 6.87 (2H, m, H_{C1} and H_{C9}), 6.94 (1H, t, H_{C7}), 7.08 (1H, d, H_{C6}), 7.14 (1H, m(t), H_{C8}), 7.55 (1H, dd, H_{C4}), 7.60 (1H, dd, H_{C2}), 9.76 (1H, s, CHO)	22.47 ($C_{4'}$), 26.24 ($C_{3'}$), 35.48 ($C_{2'}$), 46.29 ($C_{1'}$), 114.72 (C_1), 115.89 (C_9), 123.52 (C_7), 123.76 (C_{6a}), 124.99 (C_{4a}), 127.51 (C_8/C_6), 127.53 (C_8/C_6), 128.28 (C_4), 130.06 (C_2), 130.99 (C_3), 143.40 (C_{9a}), 150.66 (C_{1a}), 189.91 (C_{CHO})
2g	1680, 1600, 1576, 1552, 1464, 1396, 1360, 1248, 1200, 752	0.88 (3H, t, $H_{C5'}$), 1.25–1.42 (4H, m, $H_{C4'}$ and $H_{C3'}$), 1.78 (2H, m, $H_{C2'}$), 3.84 (2H, t, $H_{C1'}$), 6.85 (2H, m, H_{C1} and H_{C9}), 6.93 (1H, t, H_{C7}), 7.07 (1H, d, H_{C6}), 7.14 (1H, m(t), H_{C8}), 7.53 (1H, dd, H_{C4}), 7.59 (1H, dd, H_{C2}), 9.75 (1H, s, CHO)	13.99 ($C_{5'}$), 22.07 ($C_{4'}$), 26.40 ($C_{3'}$), 28.97 ($C_{2'}$), 47.93 ($C_{1'}$), 114.73 (C_1), 115.92 (C_9), 123.51 (C_7), 123.68 (C_{6a}), 124.91 (C_{4a}), 127.48 (C_8), 127.53 (C_6), 128.22 (C_4), 130.08 (C_2), 130.97 (C_3), 143.34 (C_{9a}), 150.65 (C_{1a}), 189.91 (C_{CHO})
2h	1684, 1600, 1576, 1552, 1468, 1440, 1368, 1485, 1200, 752	0.84 (3H, t, $H_{C7'}$), 1.27 (6H, m, $H_{C6'}$, $H_{C5'}$ and $H_{C4'}$), 1.38 (2H, t, $H_{C3'}$), 1.76 (2H, m, $H_{C2'}$), 3.81 (2H, t, $H_{C1'}$), 6.81 (2H, m, H_{C1} and H_{C9}), 6.89 (1H, t, H_{C7}), 7.03 (1H, d, H_{C6}), 7.10 (1H, m(t), H_{C8}), 7.49 (1H, dd, H_{C4}), 7.54 (1H, dd, H_{C2}), 9.73 (1H, s, CHO)	13.97 ($C_{7'}$), 22.46 ($C_{6'}$), 26.71 ($C_{2'} + C_{3'}$), 28.77 ($C_{4'}$), 31.65 ($C_{5'}$), 47.94 ($C_{1'}$), 114.72 (C_1), 115.94 (C_9), 123.47 (C_7), 123.74 (C_{6a}), 124.95 (C_{4a}), 127.40 (C_8), 127.49 (C_6), 128.07 (C_4), 129.99 (C_2), 131.07 (C_3), 143.33 (C_{9a}), 150.53 (C_{1a}), 189.61 (C_{CHO})

[a] Samples were heated to 320 K, cooled and kept at 295 K for 1 h. Spectra were taken at 295 K thereafter.

Table 3
Reaction conditions and analytical data for (10-alkyl-10*H*-phenothiazin-3-yl)methanols (**3a–h**)

Product	Method A		Method B		Melting point (Lit.) (°C)	Formula	HRMS M^+ found (M^+ calculated)	MS (*m*/*z*)
	Yield (%)	Time (h)	Yield (%)	Time (h)				
3a	58	72	92	10	131–132 (133–133.5 [19])	$C_{14}H_{13}NOS$	244.0801 (244.0796)	245, 244, 243, 242, 232, 231, 230, 229, 226, 214, 212, 211, 201, 200, 199
3b	68	48	93	8	98	$C_{15}H_{15}NOS$	258.0956 (258.0953)	259, 258, 257, 256, 242, 240, 231, 230, 229, 228, 260, 256, 213, 212, 211, 200, 199
3c	72	36	89	8	[a]	$C_{16}H_{17}NOS$	272.1123 (272.1109)	273, 272, 271, 270, 255, 254, 244, 232, 242, 231, 230, 229, 228, 213, 212, 210
3d	75	24	91	8	[a]	$C_{17}H_{19}NOS$	286.1269 (286.1266)	287, 286, 285, 284, 269, 268, 244, 243, 242, 231, 230, 229, 228, 213, 212, 210, 200, 199
3e	75	24	92	6	43	$C_{17}H_{19}NOS$	286.1258 (286.1266)	287, 286, 285, 284, 269, 268, 244, 243, 242, 231, 230, 229, 228, 213, 212, 210, 200, 199
3f	78	18	92	5	[a]	$C_{18}H_{21}NOS$	300.1449 (300.1422)	317, 316, 302, 301, 300, 299, 298, 243, 242, 230, 229, 228
3g	73	18	90	5	[a]	$C_{18}H_{21}NOS$	300.1449 (300.1422)	317, 316, 302, 301, 300, 299, 298, 243, 242, 230, 229, 228
3h	75	15	88	5	[a]	$C_{20}H_{25}OS$	328.1758 (328.1735)	329, 328, 327, 311, 310, 299, 243, 242, 230, 229, 228, 212, 197

[a] Semisolid.

Table 4
Spectral data for (10-alkyl-10*H*-phenothiazin-3-yl)methanols (**3a–h**)

Product	IR (KBr) ν (cm^{-1})	^1H NMR ($CDCl_3$) δ (ppm), J (Hz)	^{13}C NMR ($CDCl_3$) δ (ppm)
3a	3432, 2984, 1464, 1332, 1288, 1260, 1200, 1144, 1048, 760	[325 K]: 3.33 (3H, s, $C_{1'}$), 4.54 (~1.5H, s, CH_2–O), 6.74 (1H, d, C_1), 6.77 (1H, d, C_9), 6.90 (1H, t, C_7), 7.11 (3H, br, C_2, C_4, C_6), 7.14 (1H, t, C_8); minor signals: 3.39 (CH_3), 4.38 (CH_2–O), 4.48 (CH_2–O)	[325 K]: 35.32 ($C_{1'}$), 64.64 (CH_2–O), 113.99 (C_1/C_9), 114.05 (C_1/C_9), 122.45 (C_7), 123.28 (C_{6a}), 123.49 (C_{4a}), 126.03 (C_2/C_4), 126.34 (C_2/C_4), 127.16 (C_6/C_8), 127.47 (C_6/C_8), 135.23 (C_3), 145.37 (C_{1a}), 145.73 (C_{9a}); minor signals: 45.80 ($C_{1'}$), 122.69, 127.55, 127.88
3b	3320, 2984, 1464, 1328, 1288, 1240, 1216, 1132, 1008, 756	[325 K]: 1.38 (3H, t, $C_{2'}$), 3.88 (2H, q, $C_{1'}$), 4.51 (~1.5H, s, CH_2–O), 6.79 (1H, d, C_1), 6.82 (1H, d, C_9), 6.87 (1H, t, C_7), 7.09 (3H, br, C_2, C_4, C_6), 7.11 (1H, t, C_8); minor signals: 4.36 (CH_2–O), 4.46 (CH_2–O)	[325 K]: 13.01 ($C_{2'}$), 41.88 ($C_{1'}$), 64.60 (CH_2–O), 115.04 (C_1/C_9), 115.08 (C_1/C_9), 122.35 (C_7), 124.25 (C_{6a}), 124.75 (C_{4a}), 126.18 (C_2/C_4), 126.21 (C_2/C_4), 127.26 (C_6/C_8), 127.35 (C_6/C_8), 135.09 (C_3), 144.45 (C_{1a}), 144.90 (C_{9a}); minor signals: 45.81 ($C_{1'}$), 71.18 (CH_2–O), 114.92, 115.00, 115.20, 122.31, 122.56, 124.56, 127.01, 127.22, 127.56, 127.70, 132.34, 144.92
3c	3352, 2960, 1496, 1468, 1336, 1288, 1248, 1232, 1136, 1008, 748	[300 K[a]]: 0.95 (3H, t, $C_{3'}$), 1.76 (2H, m, $C_{2'}$), 3.74 (2H, bm, $C_{1'}$), 4.45 (~1.7H, bs, CH_2–O), 6.74 (1H, d, C_1), 6.79 (1H, d, C_9), 6.86 (1H, t, C_7), 7.04 (1H, ~d, C_2), 7.05 (1H, s, C_4), 7.08 (1H, ~d, C_6), 7.10 (1H, ~t, C_8); minor signal: 4.34 (~0.3H, bs, CH_2–O)	[300 K[a]]: 11.28 ($C_{3'}$), 20.04 ($C_{2'}$), 49.08 ($C_{1'}$), 64.32 (CH_2–O), 115.27 (C_1/C_9), 115.33 (C_1/C_9), 122.27 (C_7), 124.54 (C_{6a}), 124.91 (C_{4a}), 126.12 (C_2/C_4), 126.17 (C_2/C_4), 127.16 (C_6/C_8), 127.32 (C_6/C_8), 134.97 (C_3), 144.56 (C_{1a}), 145.14 (C_{9a}); minor signals: 53.44 ($C_{1'}$), 71.08 (CH_2–O), 115.19, 124.83 (C_{4a}), 127.02, 127.04, 132.11 (C_3), 144.72 (C_{1a})
3d	3352, 2960, 1496, 1468, 1332, 1288, 1244, 1216, 1136, 1040, 748	[300 K[a]]: 0.91 (3H, t, $C_{4'}$), 1.42 (2H, m, $C_{3'}$), 1.75 (2H, m, $C_{2'}$), 3.80 (2H, bm, $C_{1'}$), 4.50 (~1.7H, bs, CH_2–O), 6.78 (1H, ~d, C_1), 6.81 (1H, ~d, C_9), 6.87 (1H, ~t, C_7), 7.08 (3H, s + m, $C_2/C_4/C_6$), 7.11 (1H, ~t, C_8); minor signal: 4.36 (~0.2H, bs, CH_2–O)	[300 K[a]]: 13.80 ($C_{4'}$), 20.13 ($C_{3'}$), 28.94 ($C_{2'}$), 47.09 ($C_{1'}$), 64.51 (CH_2–O), 115.30 (C_1/C_9), 115.34 (C_1/C_9), 122.32 (C_7), 124.62 (C_{6a}), 125.10 (C_{4a}), 126.17 (C_2/C_4), 126.26 (C_2/C_4), 127.20 (C_6), 127.38 (C_8), 134.98 (C_3), 144.78 (C_{1a}), 145.22 (C_{9a}); minor signals: 71.14 (CH_2–O), 115.19, 127.03
3e	3400, 2952, 1496, 1464, 1336, 1256, 1244, 1232, 1144, 1104, 1012, 736	[300 K[a]]: 0.96 (6H, d, $C_{3'}$), 2.16 (1H, m, $C_{2'}$), 3.60 (2H, b, $C_{1'}$), 4.47 (~1.7H, bs, CH_2–O), 6.81 (2H, m, C_1/C_9), 6.84 (1H, m, C_8), 7.13 (4H, bm, $C_2/C_4/C_6/C_8$); minor signal: 4.38 (~0.3H, bs, CH_2–O)	[300 K[a]]: 20.12 ($C_{3'}$), 25.41 ($C_{2'}$), 55.12 ($C_{1'}$), 64.54 (CH_2–O), 115.82 (C_1/C_9), 122.42 (C_7), 125.82 (C_{6a}), 126.13 (C_2/C_4), 126.97 (C_2/C_4), 127.12 (C_6), 127.46 (C_8), 135.00 (C_3), 145.31 (C_{9a}), 145.77 (C_{1a}); minor signals: 45.88 ($C_{1'}$), 71.23 (CH_2–O), 115.71
3f	3344, 2952, 1496, 1468, 1328, 1288, 1248, 1216, 1136, 1104, 1040, 748	[325 K]: 0.94 (6H, d, $C_{4'}$), 1.68 (2H, m, $C_{2'}$), 1.72 (1H, m, $C_{3'}$), 3.84 (2H, bm, $C_{1'}$), 4.55 (~1.4H, b, CH_2–O), 6.80 (1H, ~d, C_1), 6.84 (1H, ~d, C_9), 6.88 (1H, bm, C_7), 7.12 (4H, bs, $C_2/C_4/C_6/C_8$); minor signal: 4.48 (CH_2–O)	[325 K]: 22.57 ($C_{4'}$), 26.38 ($C_{3'}$), 35.90 ($C_{2'}$), 45.85 ($C_{1'}$), 64.73 (CH_2–O), 115.37 (C_1/C_9), 115.40 (C_1/C_9), 122.40 (C_7), 124.86 (C_{4a}), 125.42 (C_{6a}), 126.20 (C_2), 126.35 (C_4), 127.25 (C_6), 127.47 (C_8), 135.10 (C_3), 144.92 (C_{1a}/C_{9a}); minor signals: 68.29 (CH_2–O), 115.48, 127.68
3g	3350, 2952, 1496, 1468, 1336, 1288, 1252, 1208, 1136, 1104, 748	[300 K[a]]: 0.87 (3H, t, $C_{5'}$), 1.32 (2H, m, $C_{4'}$), 1.37 (2H, m, $C_{3'}$), 1.76 (2H, m, $C_{2'}$), 3.79 (~1.5H, b, $C_{1'}$), 4.50 (~1.5H, b, CH_2–O), 6.77 (1H, m, C_1), 6.82 (1H, m, C_9), 6.87 (1H, t, C_7), 7.08 (2H, bs, C_2/C_4), 7.10 (1H, m, C_8)	[300 K[a]]: 14.04 ($C_{5'}$), 22.34 ($C_{4'}$), ~26.5 (b, $C_{2'}$), 29.12 ($C_{3'}$), ~47.4 (b, $C_{1'}$), 64.47 (CH_2–O), 115.26 (C_1/C_9), 115.31 (C_1/C_9), ~122.3 (b, C_7), ~124.9 (b, C_{4a}), 126.16 (C_2/C_4), 127.18 (C_6), ~127.4 (b, C_7), ~135.0 (b, C_3), 144.67 (C_{1a}/C_{9a})
3h	3320, 2928, 1496, 1468, 1336, 1288, 1244, 1216, 1136, 1104, 1040, 744	[325 K]: 0.86 (3H, t, $C_{7'}$), 1.26 (4H, bs, $C_{6'}$ and $C_{5'}$), 1.29 (2H, m, $C_{4'}$), 1.40 (2H, m, $C_{3'}$), 1.77 (2H, m, $C_{2'}$), 3.80 (~1.6H, bs, $C_{1'}$), 4.51 (~1.6H, s, CH_2–O), 6.78 (1H, ~d, C_1), 6.81 (1H, ~d, C_9), 6.86 (1H, bm, C_7), 7.08 (4H, bs, $C_2/C_4/C_6/C_8$)	[325 K]: 14.01 ($C_{7'}$), 22.54 ($C_{6'}$), 26.95 ($C_{3'}/C_{2'}$), 28.93 ($C_{4'}$), 31.77 ($C_{5'}$), 47.58 ($C_{1'}$), 64.62 (CH_2–O), 115.36 (C_1/C_9), 115.40 (C_1/C_9), 122.37 (C_7), 124.77 (C_{4a}/C_{6a}), 126.17 (C_2), 126.28 (C_4), 127.22 (C_6), 127.41 (C_8), 135.13 (C_3), 144.88 (C_{1a}/C_{9a}); minor signals: 115.23, 127.00, 127.63

[a] After heating to 325 K and cooling.

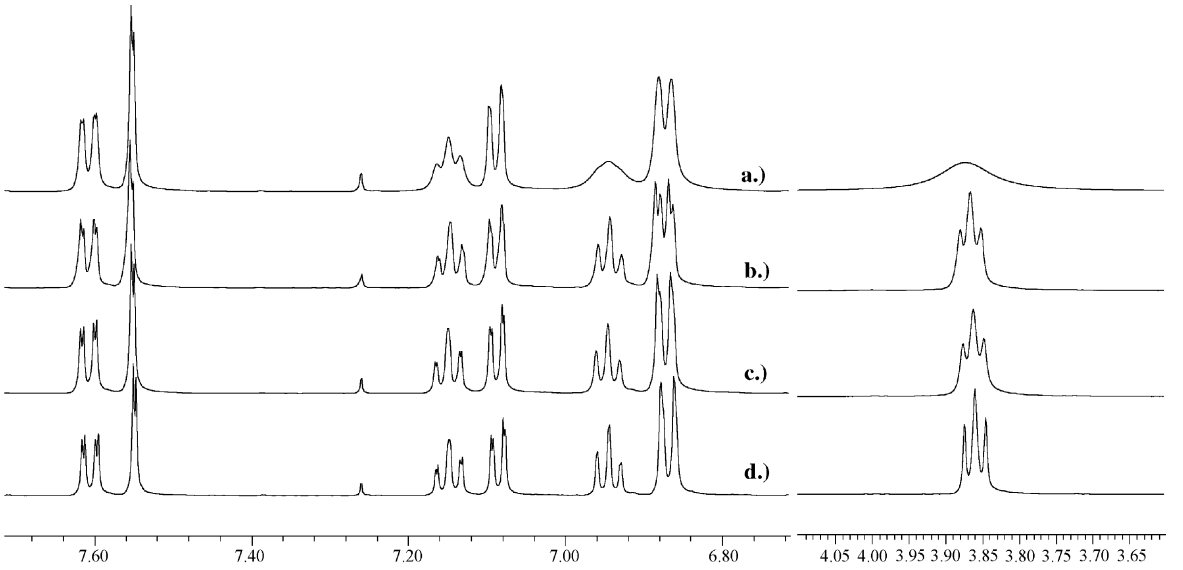

Fig. 2. ^{1}H NMR spectra of 10-butyl-10*H*-phenothiazine-3-carbaldehyde (**2d**): (a) at 295 K after dissolving the sample in $CHCl_3$; (b) at 320 K; (c) 1 h after cooling to 295 K; (d) 48 h after cooling to 295 K.

toluene as eluent). After the reaction completed, Amberlite XAD-7 adsorbent (10 g) was added and the stirring was continued for 5 min. The polymeric beads were filtered off from the suspension on 100 μm filter. The beads were washed by water (100 ml) and dried under IR lamp. Desorption of the product from the polymeric beads was performed by acetone (50 ml, three times; the polymeric beads might be reused after this process). The combined acetone solutions were concentrated in vacuum and the residue was purified by column chromatography on silica gel, using toluene–acetone (9:1) as eluent. Reaction details and physical data for the resulting (10-alkyl-10*H*-phenothiazin-3-yl)methanols (**3a**–**h**) are given in Tables 3 and 4.

3. Results and discussion

The 10-alkyl-10*H*-phenothiazine-3-carbaldehydes (**2a**–**h**) were conveniently prepared by the simple Vilsmeier–Haack formylation (*N*,*N*-dimethylformamide/$POCl_3$) of the corresponding 10-alkyl-10*H*-phenothiazines (**1a**–**h**) [25] (Fig. 1, Table 1).

The new compounds were unambiguously characterized by their IR, MS, HRMS and NMR (including multidimensional HMBC, HMQC experiments) data (see Section 2). The signal broadening found during the NMR experiments with the phenothiazine carbaldehydes (**2a**–**h**) deserves comment (see Fig. 2 for the ^{1}H NMR specra of **2d**).

Such signal broadening might be caused either by hindered rotation of the *N*-alkyl moiety or by molecular associations. If the hindered rotation is responsible for the signal broadening, the signals should be sharpen at higher temperature but broaden again at lower temperature. Since the signals (Fig. 2a) sharpened at higher temperature (Fig. 2b), but did not broadened again on cooling back (Fig. 2c), the original signal broadening was not a consequence of hindered rotation around N–C bond. It might be assumed therefore, that these phenothiazine-3-carbaldehydes (**2a**–**h**) dissolve in $CDCl_3$ as molecular associates—most probably as dimers—and transform slowly into monomeric species showing sharp signals in their NMR spectrum (Fig. 2d).

Since $NaBH_4$ was used for reduction of various heterocyclic aldehydes like 6-bromopyridine-2-carbaldehyde [26], quinoline-2-carbaldehyde [27], 2-chlo-

roquinoline-3-carbaldehyde [28] or 1,10-phenanthrolin-4-carbaldehyde [29] leading to the corresponding alcohols in high yield, this reagent was tried with the 10-alkyl-10*H*-phenothiazine-3-carbaldehydes (**2a**–**h**) as well. Surprisingly, the $NaBH_4$ reduction of this phenothiazine-3-carbaldehydes (**2a**–**h**) proved to be quite slow and was always accompanied by formation of several unidentified by-products which required purification by preparative chromatography. Hence, the desired alcohols (**3a**–**h**) were obtained in moderate yields by this method.

The stereoselective reduction of various aldehydes by baker's yeast—resulting the corresponding alcohols smoothly—is a known process [30]. Therefore, it seemed worthwhile to try this mild method for the reduction of the 10-alkyl-10*H*-phenothiazine-3-carbaldehydes (**2a**–**h**), too. Fortunately, this biotransformation proved to be not only mild but also effective and yielded the desired alcohols (**3a**–**h**) as the sole products. Several work-up methods were tested for isolating the products in high yields from the complex reaction mixture of the baker's yeast reduction. Adsorption of the product on non-ionic polymeric adsorbent XAD-7 followed by filtration–desorption proved to be the most convenient work-up method providing easy and high yield recovery of the product from the reaction mixture.

Interestingly, after dissolving in $CDCl_3$ broad signals in the NMR spectra of the (phenothiazine-3-yl)-methanols (**3a**–**h**) were observed. This broad signals also sharpened on heating, but at higher temperature as well as after cooling NMR spectra indicated the presence of a major and one or more minor species (see NMR data in Table 4). In this case, it can be proposed, that the (phenothiazine-3-yl)methanols (**3a**–**h**) dissolve in $CDCl_3$ as molecular associates, but these original associates resembling the solid state packing transform into the major monomeric species and due to the strong O–H . . . N bonding new dimeric minor species.

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